Wills Eye Resident Series: A woman presents with suspected neuroretinitis, *p. 70*

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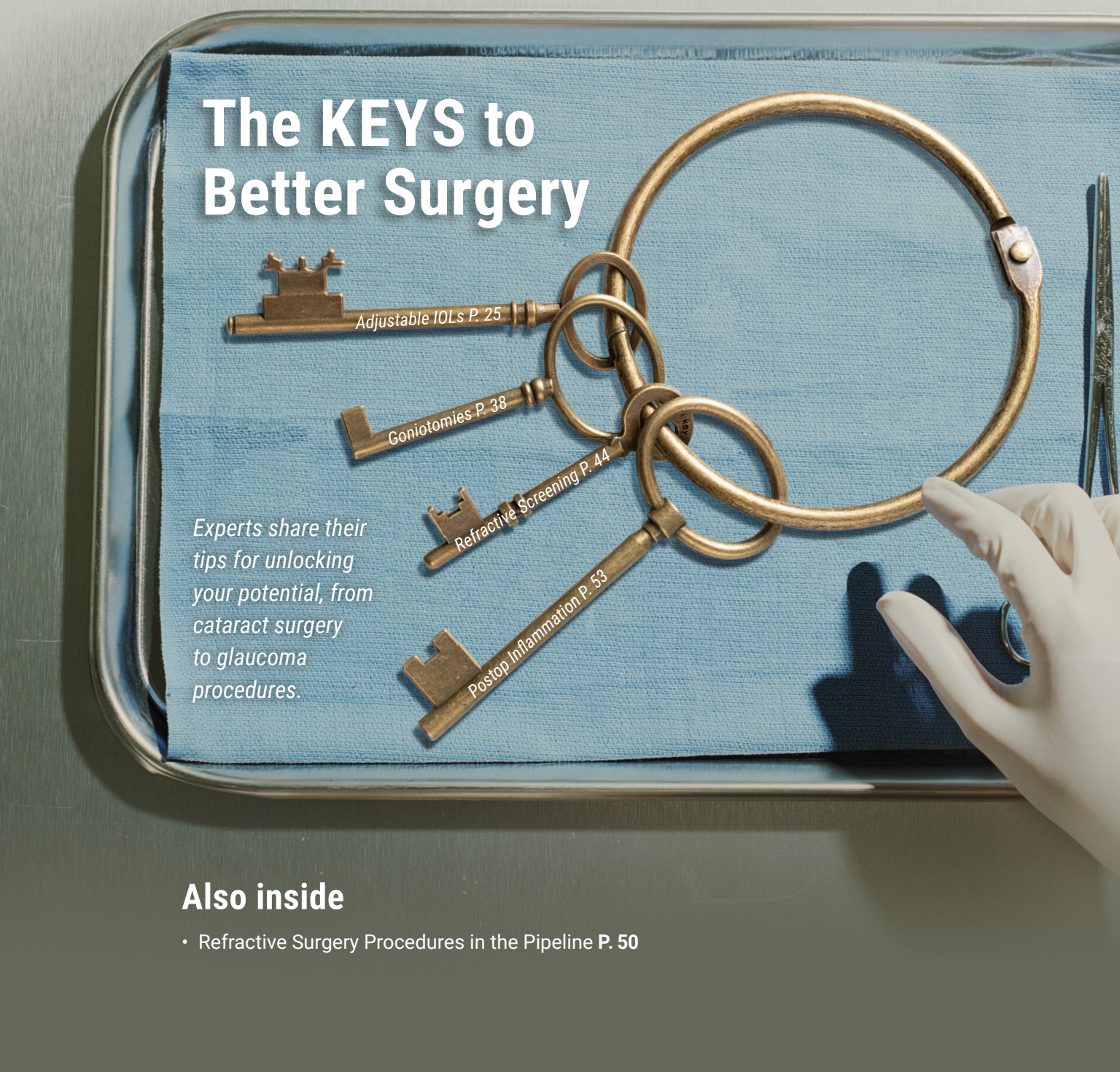

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VABYSMO™ (faricimab-svoa) is the only treatment that delivers powerful **first-line efficacy** with **1–4 month dosing**[1-5*†]

*Primary endpoint of non-inferiority vs aflibercept was defined as the mean change from baseline in BCVA (measured by the ETDRS letter score) to 1 year (average of weeks 40, 44, and 48 in nAMD and weeks 48, 52, and 56 in DME) and was tested for non-inferiority using a margin of 4 letters.[1]
†After 4 or 6 monthly loading doses.[1] Please see below for more information.
‡Verana Health data from Q1–Q4 2022.[6]

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†Dosing Information:
DME dosing: at least 4 monthly loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual acuity evaluations OR 6 monthly loading doses followed by Q8W. Q4W dosing may be needed (no added benefit). nAMD dosing: 4 monthly loading doses followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform Q16W (weeks 28 and 44), Q12W (weeks 24, 36, and 48), Q8W (weeks 20, 28, 36, and 44), or Q4W (no added benefit) dosing.[1]

INDICATIONS

VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular infection, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

Warnings and Precautions

Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.

Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO. Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see Brief Summary of full VABYSMO Prescribing Information on the following page.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023. **2.** Beovu® (brolucizumab-dbll) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2022. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **6.** Data on file. South San Francisco, CA: Genentech, Inc.

BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

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This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1,262	AMD N=662	DME N=625
Cataract	3%	15%	2%	12%
Conjunctival hemorrhage	7%	8%	8%	7%
Vitreous floaters	3%	4%	2%	3%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	4%	2%	3%
Eye pain	3%	3%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	< 1%	< 1%	1%
Lacrimation increased	1%	1%	1%	< 1%
Ocular discomfort	1%	1%	< 1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO™ [faricimab-svoa]
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Buckling May Be Preferred in Macula-off Detachments

For patients with macula-off primary rhegmatogenous retinal detachments, scleral buckling may be the wiser repair approach, according to a recent study published in *BMC Ophthalmology*. At present, primary RRDs are typically addressed using scleral buckling, pars plana vitrectomy, combined scleral buckling and pars plana vitrectomy, and pneumatic retinopexy. However, despite successful repair, it's not uncommon for some eyes to go on to develop complications such as cystoid macular edema or epiretinal membrane. The study authors investigated and compared incidence rates and risk factors associated with CME and ERM after primary RRD repair with scleral buckling and pars plana vitrectomy. They reported that macular status and repair approach play a role in risk.

The retrospective observational cohort study included 62 consecutive patients with primary RRD who were treated with either scleral buckling or pars plana vitrectomy. Those who underwent scleral buckling were young, phakic patients without posterior vitreous detachment, high myopic patients and those whose RRD was associated with anterior or interior retinal tears.

Patients who underwent pars plana vitrectomy were pseudophakic or had media opacity and posterior breaks precluding scleral buckling use. Macular changes were evaluated at the three- and six-month postop visits. For phakic patients whose media opacity or lens bulging hindered surgical maneuvers, phacoemulsification and IOL implantation was also performed.

Inner limiting membrane peeling, a non-standard surgical procedure for RRD repair but one that's been reported to confer greater macular elasticity during reattachment, was performed randomly in the macula-off (15/30 patients) and the macula-on RRD "pending foveal detachment" (2/4 patients) subgroup.

Study co-author Matteo Ripa, MD, of the Department of Ophthalmology, William Harvey Hospital, East Kent Hospitals University NHS Foundation Trust in the United Kingdom, explains that surgeons should consider macular status to be a critical factor requiring constant evaluation in "primary retinal detachment repair management due to its role in determining final visual and functional outcomes." He says, "Assessing the risk factors and incidence of ERM and CME formation after scleral buckling and pars plana vitrectomy in patients who developed primary RRD, we found that macula-off status significantly increased the risk of CME by odds-ratio (OR)=4.3 times compared with macula-on, regardless of the procedure (p=0.04), whereas neither the macula-off status in patients who underwent pars plana vitrectomy nor the ILM peeling significantly increased the risk of postoperative CME (OR=1.73, p=0.4 and OR=1.8, p=0.37, respectively).

"Furthermore, our results clearly show significant differences in CME incidence when comparing patients who underwent pars plana vitrectomy and scleral buckling (i.e., 33 percent of patients (14/42) who underwent pars plana vitrectomy developed a postoperative CME, and no CME cases were found in the scleral buckling group, p=0.001)," he continues. "At the end of the follow-up, resolution of CME was observed in 13 out of 14 patients (92.86 percent). Despite the treatment (indomethacin three times daily up to resolution), CME didn't resolve in only one patient.

"Regarding the OCT CME morphology, we mostly found central cystoid spaces within the inner or outer retina ± subretinal fluid with no diffuse macular distribution," he says. "Furthermore, according to the CME morphology, only six cases of CME were associated with ERM. Several factors could have been implied in the CME genesis, such as inflammation, tractions and macular status. Nonetheless, inflammation played a crucial role, as eight out of 14 (57.14 percent) cases of CME weren't associated with ERM (a possible additional tractional mechanism)."

When asked about phacovit-

(Continued on p. 8)

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Detachment Repair

rectomy for RRD repair, Dr. Ripa noted that this combined procedure has several advantages but may be unsuitable for certain patients. He explains, "First, in patients with significant cataracts, a combined procedure in which the surgeon addresses the cataract first optimizes the view and surgical access to the retina, thus improving the visualization for more detailed retinal work. Second, it leads to an overall faster recovery time as pars plana vitrectomy can induce lens opacification that's most likely to occur in a reasonably short time, thus affecting postoperative visual recovery. Third, it eases surgical maneuvers reducing the so-called 'lens touch' that may lead to increased complication rates in subsequent cataract surgery. Moreover, despite a high risk of 'refractive surprise,' many surgeons remove the natural lens in combination with the pars plana vitrectomy, regardless of the cataract.

"Despite these several advantages, the higher risk of CME after combined surgeries cannot be underrated, as the postoperative inflammation can compromise functional recovery," he says. "Therefore, according to the study results, every surgeon should balance the benefits and risks to properly manage primary retinal detachment repair using a more personalized therapeutic approach."

Dr. Ripa points out that study limitations included its retrospective, non-randomized nature and small sample size (62 patients, 20 in scleral buckling, and 42 in pars plana vitrectomy subgroups); that it didn't "consider a multivariate analysis of several risk factors for CME and the ERM development after primary RRD repairs, such as age, extensive vs. not extensive use of endolaser retinopexy or cryotherapy, type of tamponade used, possible additional surgical maneuvers, number of previous surgeries and RRD surgery duration. In addition, the retinal tears numbers and their location weren't considered as a deciding factor for the surgical technique adopted"; that "ILM peeling was performed on macula-off and macula-on 'pending foveal detachment' but not in macula-on 'properly so-called' "; and that "six-month outcomes may not necessarily indicate long-term outcomes, as ERM and CME may arise long after a successful primary RRD repair."

Overall, he advises surgeons to consider macular status when approaching primary retinal detachment repair since this factor had such a significant effect on postoperative complications, independent of surgical technique. He says, "Scleral buckling may be less likely to be related to postoperative surgical complications than pars plana vitrectomy in achieving surgical primary RRD repair, according to other research that reported a higher risk of CME associated with any *ab-interno* macular surgery."

Physicians Deal with Corneal Infections from Artificial Tears

Amid a nationwide recall of Global Pharma Health Care's artificial tears (sold under the names EzriCare and Delsam Pharma) due to the products' possible contamination, ophthalmologists at Bascom Palmer published a report on a patient whose infection may be linked to the agent[1]. As of mid-March, according to the Centers for Disease Control and Prevention, 68 patients in 16 states have been infected with a rare strain of extensively drug-resistant *P. aeruginosa*. Three patients have died and there have been eight reports of vision loss and four enucleations due to the infections. The CDC adds that isolates were identified from cultures of sputum or bronchial wash (15), cornea (17), urine (10), other nonsterile sources (4), blood (2), and from rectal swabs (26). Some patients had specimens collected from more than one site.

In the study, the researchers recount how an older man presented with complaints of right eye pain and decreased vision that had lasted for the past day. His medical history included coronary artery disease, diabetes and chronic obstructive pulmonary disease. He wore contact lenses but denied sleeping in them or overuse. He also reported the use of EzriCare artificial tears. His best-corrected visual acuity was hand motion in the right eye and 20/20 in the left. Intraocular pressures were 29 mmHg in the right eye and 14 mm Hg in the left. In the patient's right eye, the physician noted conjunctival hyperemia, a 6×5-mm corneal infiltrate with overlying epithelial defect, and 2-mm hypopyon. Ultrasound was normal without membranes or vitritis.

The authors say that, since there's currently a rash of multi-drug resistant infections due to the use of EzriCare drops and a recent CDC warning about the situation, they treated the eye with with topical fortified vancomycin, fortified tobramycin and trimethoprim-polymyxin drops every hour while awake. They cultured both the infiltrate and the EzriCare artificial tears. The corneal culture was positive for *P. aeruginosa* with high resistance to fluoroquinolones; aminoglycosides, including amikacin and tobramycin; and cephalosporins, with moderate carbapenem resistance

(Continued on p. 16)

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†Out of 124 patients from the clinical study, 122 responded that they would have LASIK again.

References

1. Lobanoff M, Stonecipher K, Tooma T, et al. Clinical outcomes after topography-guided LASIK: comparing results based on a new topography analysis algorithm with those based on manifest refraction. *J Cataract Refract Surg*. 2020;46(6):814-819. doi:10.1097/j.jcrs.0000000000000176.

2. Stulting RD, Fant BS; T-CAT Study Group. Results of topography-guided laser in situ keratomileusis custom abalation treatment with a refractive excimer laser. *J Cataract Refract Surg*. 2016;42(1):11-18. Study description: Prospective, nonrandomized, multicenter study of 249 eyes with myopia (up to -9D) or myopic astigmatism of 6.0 D or less. Outcome measures included manifest refraction, UDVA, CDVA and visual symptoms up to 12 months.

For Important Product Information about Contoura® Vision, please refer to the adjacent page.

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Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System. **Indications**: FDA has approved the WaveLight® Excimer Laser systems for use in laser-assisted in situ keratomileusis (LASIK) treatments for: the reduction or elimination of myopia of up to - 12.00 D and up to 6.00 D of astigmatism at the spectacle plane; the reduction or elimination of hyperopia up to + 6.00 D with and without astigmatic refractive errors up to 5.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.00 D; the reduction or elimination of naturally occurring mixed astigmatism of up to 6.00 D at the spectacle plane; and the wavefront-guided reduction or elimination of myopia of up to -7.00 D and up to 3.00 D of astigmatism at the spectacle plane. In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of up to -9.00 D of myopia, or for the reduction or elimination of myopia with astigmatism, with up to -8.00 D of myopia and up to 3.00 D of astigmatism. The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia. **Contraindications**: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who: are pregnant or nursing; have a diagnosed collagen vascular, autoimmune or immunodeficiency disease; have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*); have severe dry eye; have corneas too thin for LASIK; have recurrent corneal erosion; have advanced glaucoma; or have uncontrolled diabetes. **Warnings**: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have: systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status; a history of Herpes simplex or Herpes zoster keratitis; significant dry eye that is unresponsive to treatment; severe allergies; a history of glaucoma; an unreliable preoperative wavefront examination that precludes wavefront-guided treatment; or a poor quality preoperative topography map that precludes topography-guided LASIK treatment. The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment. Topography-guided LASIK requires preoperative topography maps of sufficient quality to use for planning a topography-guided LASIK treatment. Poor quality topography maps may affect the accuracy of the topography-guided LASIK treatment and may result in poor vision after topography-guided LASIK. **Precautions**: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with: progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone; corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage; residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia; pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning; history of glaucoma or ocular hypertension of > 23 mmHg; taking the medications sumatriptan succinate (Imitrex*); corneal, lens and/or vitreous opacities including, but not limited to cataract; iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or taking medications likely to affect wound healing including (but not limited to) antimetabolites. In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for: treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted; In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population. Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery. **Adverse Events and Complications** Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination. The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect. Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination. The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface. Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees. The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort, one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye. The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort. Topography-Guided Myopia: There were six adverse events reported in the topography-guided myopia study. Four of the eyes experienced transient or temporary decreases in vision prior to the final 12 month follow-up visit, all of which were resolved by the final follow-up visit. One subject suffered from decreased vision in the treated eye, following blunt force trauma 4 days after surgery. One subject experienced retinal detachment, which was concluded to be unrelated to the surgical procedure. **Clinical Data** Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes that were eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline). Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months. Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%). Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months. Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline). Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%. Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20. In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline). Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months. Topography-Guided Myopia: The topography-guided myopia clinical study included 249 eyes treated, of which 230 eyes were followed for 12 months. Accountability at 3 months was 99.2%, at 6 months was 98.0%, and at 12 months was 92.4%. Of the 247 eyes that were eligible for the UCVA analysis at the 3-month stability time point, 99.2% were corrected to 20/40 or better, and 92.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "marked" or "severe" at an incidence greater than 5% at 1 month after surgery: dryness (7% vs. 4% at baseline) and light sensitivity (7% vs. 5% at baseline). Visual symptoms continued to improve with time, and none of the visual symptoms were rated as being "marked" or "severe" with an incidence of at least 5% at 3 months or later after surgery. Long term risks of topography-guided LASIK for myopia with and without astigmatism have not been studied beyond 12 months. **Information for Patients:** Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries. **Attention:** Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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FEATURES

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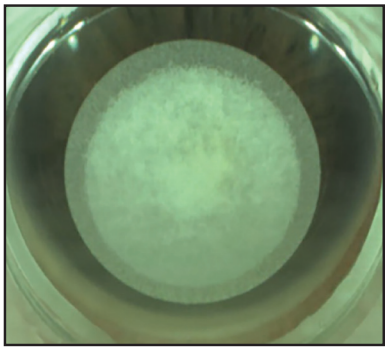
Cover Focus



DEPARTMENTS

April 2023

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ENOUGH
IS ENOUGH
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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

The Chatbots Are Coming!

A few years ago, at a holiday party, I ran into the husband of one of my wife's friends, and in the course of conversation, asked him how his job was going. "Great," he said, "I'm training my replacement." Turns out, the tech company he worked for was looking to outsource his job to another country, where labor costs were lower, and was having him show the ins and outs of his position to someone in the outsource facility. Merry Christmas!

In February of this year, a group of researchers reported that, for the first time ever, ChatGPT, a "language-based" artificial intelligence, performed at or near the passing threshold (60-percent) on the United States Medical Licensing Exam.[1] It did this without any human assistance or a connection to the internet. The authors called this a "surprising and impressive result," especially in light of the fact that, only months earlier, the best it could muster was 36.7 percent. Hearing this, I couldn't help but think of my friend training his replacement.

I think artificial intelligence is a wonderful tool that's already being used as a useful adjunct in spot duty, catching abnormalities on screening images to help physicians treat more people at a more efficient pace, for example. But that's a very specific use, like a wrench. An AI that can analyze a variety of complex patient presentations from various specialties, develop a diagnosis and formulate the proper treatment plan is a different story entirely. That's not just a wrench—it's the whole toolbox. It's what physicians do.

Now, I'm not paranoid about artificial intelligence replacing physicians, but I think it's worth going into the future of AI with our eyes open to all the possibilities—both positive and negative. Why? Because a health-insurance company never met a cost-cutting measure it didn't like. What if, at some point in the not-so-distant future, the insurance company discovered that a chatbot could perform clinical tasks as well as, or better than, a human physician? As a bean-counter bonus, the chatbot never sleeps, and doesn't take lunches, vacations or sick days.

This probably won't be happening any time soon, though, because it appears that ChatGPT costs about $100,000 per day to run[2]. Also, when I queried ChatGPT about AIs replacing physicians, it acknowledged that, "Human doctors have important qualities such as empathy, creativity, and the ability to understand complex social and cultural factors that may affect patient health. These qualities are not easily replicated by machines and are an essential part of the health-care system." It lacks the human touch.

I don't know the answers to all these questions—and maybe it'll all be OK in the end—but, as the researchers in the ChatGPT study wrote: The AIs are evolving at an ever-rapid rate. Maybe our ruminations about them should accelerate too.

— Walter Bethke
Editor in Chief

1. Kung TH, Cheatham M, Medenilla A, et al. Performance of ChatGPT on USMLE: Potential for AI-assisted medical education using large language models. PLOS Digital Health. February 9, 2023 (online article). https://doi.org/10.1371/journal.pdig.0000198.
2. Goodwin R. ChatGPT is VERY Expensive To Run – Here's Why... KYM. January 24, 2023 (online article).

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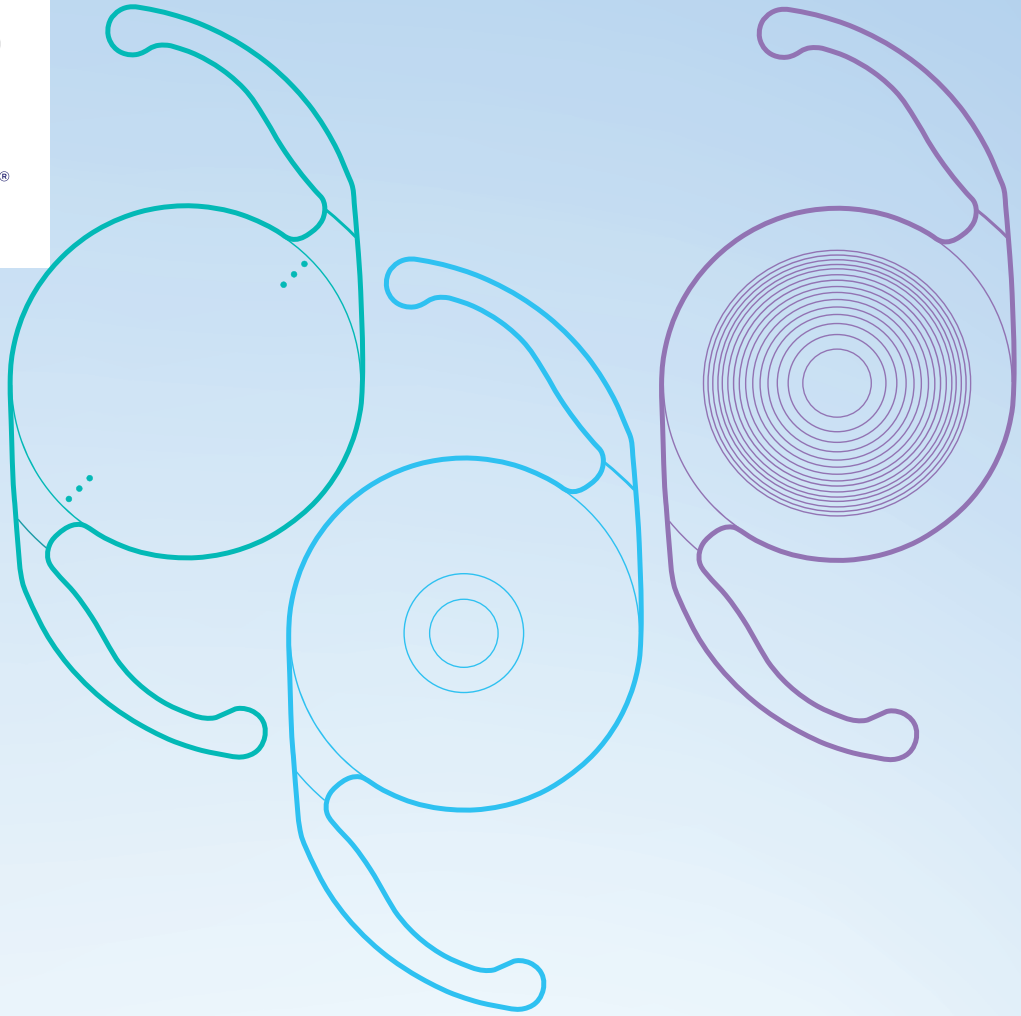

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† In vitro comparison, P <0.05.
‡ Results from a prospective, randomized, parallel group, subject- and assessor-masked, multisite trial of 107 subjects bilaterally implanted with the AcrySof® IQ Vivity® Extended Vision IOL and 113 with the AcrySof® IQ IOL with 6 months follow-up.
¶ Snellen VA was converted from logMAR VA. A Snellen notation of 20/20-2 or better indicates a logMAR VA of 0.04 or better, which means 3 or more of the 5 ETDRS chart letters in the line were identified correctly.
§ N=297.
|| Q4 2022.

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REVIEW NEWS

(Continued from p. 8)

Corneal Infection

(minimum inhibitory concentration = 4). The EzriCare culture was also positive for *P. aeruginosa* resistant to fluoroquinolones, aminoglycosides, and cephalosporins, with higher carbapenem resistance (minimum inhibitory concentration = 8). Based on the bacterial sensitivities, they say that the patient was continued on trimethoprim-polymyxin every hour and switched to imipenem-cilastatin every two hours, "as this antibiotic class had the lowest resistance of those tested." The patient is currently undergoing treatment with close monitoring, as he had persistent infection and vision loss at his last follow-up, the researchers say.

In a commentary on the outbreak in *JAMA Ophthalmology*, Kathryn Kolby, MD, PhD, chair of the department of Ophthalmology at the NYU Grossman School of Medicine, writes, "… the current outbreak of Verona Integron-mediated Metallo-ß-lactamase (VIM) and Guiana-Extended Spectrum-ß-Lactamase (GES)-producing carbapenem-resistant (VIM-GES-CRPA), a rare strain of extensively drug-resistant *Pseudomonas aeruginosa*, associated with the use of carboxymethylcellulose sodium (EzriCare) multidose preservative-free artificial tears may be a wake-up call for the field. … This outbreak is a harsh reminder that all eye drops, including artificial tears, are medications with potential adverse effects, most commonly ocular but potentially systemic." ◀

1. Shoji MK, Gutkind NE, Meyer BI, et al. Multidrug-Resistant Pseudomonas aeruginosa Keratitis Associated With Artificial Tear Use. JAMA Ophthalmol. March 22, 2023 (online article).

INDUSTRY NEWS

Aurion Receives Approval In Japan

Aurion Biotech received regulatory approval from Japan's Pharmaceuticals and Medical Devices Agency for its novel cell therapy, Vyznova, for the treatment of bullous keratopathy of the cornea. The company believes this is the first-ever regulatory approval in the world for an allogeneic cell therapy to treat corneal endothelial disease.

The breakthrough innovation of this cell therapy is to enable fully differentiated corneal endothelial cells to regenerate outside the body, the company says.

Healthy cells from a donor cornea are cultured in a novel, multi-step, proprietary and patented process that produces off-the-shelf, allogeneic, fully differentiated CECs. The endothelial cells are then injected intracamerally where they repopulate into a healthy mono-layer and start removing fluid from the cornea, thereby decreasing corneal edema, the company says.

Aviceda Submits Applications for Approval

Aviceda Therapeutics submitted to the Food and Drug Administration an Investigational New Drug application for its lead intravitreal ocular asset, AVD-104 (a novel glycan-coated nanoparticle) to treat geographic atrophy secondary to AMD.

Iveric Bio Gets Priority Review

Iveric Bio announced the Food and Drug Administration completed its filing review and accepted the company's New Drug Application for avacincaptad pegol, a novel investigational complement C5 inhibitor for the treatment of geographic atrophy secondary to age-related macular degeneration. The New Drug Application, based on efficacy and safety results from the GATHER1 and GATHER2 clinical trials, was granted Priority Review with a Prescription Drug User Fee Act goal date of August 19.

How to Control an Overfiltering Bleb

What to do if a cataract patient who previously had glaucoma surgery presents with this tricky scenario.

LIZ HUNTER
SENIOR EDITOR

Cataract surgeons are often faced with some unwanted yet unavoidable issues in their patients outside of cataract removal, and thus must be ready for the unexpected. One such scenario relates to cataract patients who underwent a previous glaucoma surgery and have an overfiltering trabeculectomy. Patients may present asymptomatic or with complaints of blurred vision, and it's imperative for cataract surgeons to accurately address the overfiltration and IOP with the best course of action. Failure to do so could affect IOL calculations.

We spoke with glaucoma specialists to hear how they approach these patients and their recommendations for successful visual outcomes.

Recognizing the Signs and Symptoms

The goal of any trabeculectomy is to lower the eye pressure in glaucoma patients, but sometimes, a trabeculectomy can work too well and the pressure can get too low and the patient can become hypotonous.

Overfiltration typically develops early on following the glaucoma surgery, either immediately after or after releasing the scleral flap sutures, says Jody Piltz-Seymour, MD, who is an adjunct professor at UPenn's Perelman School of Medicine and an attending at Wills Eye Hospital. However, she's also seen patients present with late overfiltration.

"One was a young man who started heavy weight lifting about three years after his trabeculectomy and he became hypotonous with the development of macula striae in his only eye," Dr. Piltz-Seymour says. "And we've seen overfiltration and hypotony develop late in some patients treated with anti-VEGF agents, but most of the time, it usually presents early in the postop period."

> **Whether you performed biometry measurements before the hypotony developed or after, there will be issues with IOL accuracy.**
>
> ***— Jody Piltz-Seymour, MD***

Patients can present in three different ways. "One is that they don't notice anything. Many eyes can tolerate a low eye pressure and the patient remains asymptomatic," Dr. Piltz-Seymour says. "But some patients with overfiltering blebs can develop bleb dysesthesia or blurred vision. Bleb dysesthesia develops when the elevated contour of the bleb interferes with how the lid interacts with the surface of the eye. Normally as we blink, the eyelids spread the tears smoothly over the corneal surface. But if you have a large, bullous bleb, as the lid passes over that bleb, it may not come in contact with the superior cornea and you get dry spots and irritation. Dellen may also develop."

Bleb dysesthesia presents with pain, irritation or foreign body sensation, continues Dr. Piltz-Seymour. "It can be a mild annoyance or severely debilitating for some people. Others can develop bubble dysesthesia, where each time they blink a little bubble forms between their lid and the limbal edge of the bleb and makes these little pops every time they blink. If overfiltration causes hypotony issues, patients may have blurred vision and this needs to be addressed to restore the patient's optimal vision," she says.

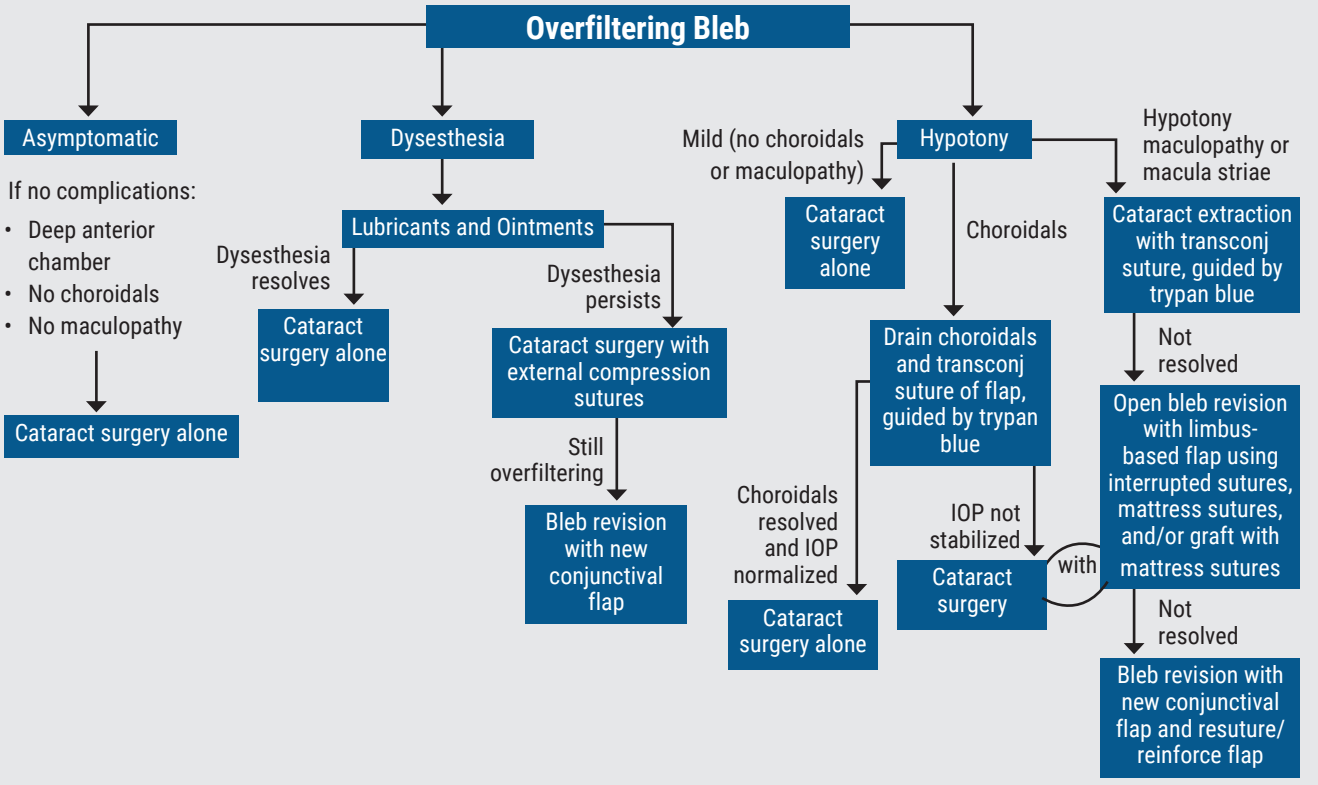
According to Erin A. Boese, MD, a clinical assistant professor of ophthalmology and visual sciences at the University of Iowa, not all hypotony is created equal. "The hard part about hypotony and overfiltering trabeculectomy is that it's not the same in everybody," she says. "There are some people out there who might do great with a pressure of 3 or 4 mmHg and not have any problems with hypotony, then there are some people who might have pressures even higher than that and still have issues. So it's really from the symptoms and exam where we differentiate the people whose pressure is too low vs. doing well."

Dr. Boese says complaints of shadows in the periphery could be caused by choroidal effusions, and

This article has no commercial sponsorship.

Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.

Overfiltering Bleb in the Presence of Cataract Decision Tree



blurred/distorted vision could be hypotony maculopathy, which would appear as wrinkling on the macula during an exam or by using OCT.

Bleb overfiltration that causes hypotony can lead to blurred vision from multiple mechanisms. "Blurred vision from overfiltration has numerous etiologies. You can sometimes see subtle vertical pooling of fluorescein on the corneal surface that I refer to as tear striae that can be associated with mild blurred vision," says Dr. Piltz-Seymour. "Hypotony can also lead to serous choroidal detachments, which usually, but not always, resolve. Patients may develop shallow anterior chambers, which can usually be treated conservatively if not severe, and there's an increased risk of cataract development with low IOPs. But the thing that's really the most detrimental to vision is hypotony maculopathy. Fine macular striae can cause marked visual compromise and if not treated in a timely fashion, can lead to permanent deficits, even if the pressure is raised. Tear striae and shallow chambers resolve if the pressure goes up, choroidals usually resolve spontaneously or can be drained, but hypotony maculopathy, if not fixed, can really cause long-term problems. You don't want to sit on hypotony maculopathy for too long."

Treatment in the Presence of a Cataract

Dr. Boese says removing a cataract with a bleb present causes a surgeon to think differently, and those considerations compound when the bleb is overfiltering. "In some people you just want to nudge their pressure up by a couple of points and in others where the pressure is way too low, you really need to just completely start new to bring it up a lot. Depending on the situation, your approach might differ," she says.

Dr. Piltz-Seymour agrees, adding that there are multiple paths the procedure could take depending on what issues the patient is experiencing due to the overfiltering bleb. *(See Decision Tree, above)*

Here are their recommendations for the possible scenarios:

• ***Treatment in asymptomatic patients.*** If the patient has no other complications and their IOP only needs to come up a slight amount, cataract surgery itself might do the trick.

"If you're just slightly low and you'd like to see that pressure come up a little bit, one of the things that you can do is take advantage of a little bit of the inflammation that comes with doing the cataract surgery," says Dr. Boese. "It's not much but you don't need a lot either. Normally if I have a well-filtering bleb—it's not overfiltering—and I do cataract surgery, afterwards I'm using lots of topical steroids, way more than I would normally to help keep that trabeculectomy function-

Multi-Specialty Perspectives on Ocular Itch Relief for Allergic Conjunctivitis

John Hovanesian, MD
Harvard Eye Associates
in Laguna Hills, CA.

Leslie O'Dell, OD
Medical Director of Medical Optometry
America in York, PA.

Bob Lanier, MD, FACAAI, FAAAI
Clinical Professor Immunology
University of North Texas Health Science
Center, Fort Worth, TX.

An estimated 66 million Americans suffer from ocular allergies.[1] In fact, ocular symptoms are second only to nasal symptoms in prevalence and itchy eyes are reportedly as bothersome as nasal congestion.[2,3] Furthermore, it's important to note that both ocular and nasal symptoms commonly present together.[2,3] In sum, patients are experiencing meaningful impacts on their quality of life as a result of seasonal allergic conjunctivitis and they seek out care from many health care specialists—from pharmacists and primary care physicians to eye doctors and allergists. Here, three specialists—an ophthalmologist, an optometrist and an allergist-immunologist—share helpful disease state and prescribing insights that can help guide decision-making and lessen the burden of disease on patients as we enter a new allergy season.

THE ALLERGIC RESPONSE

In practice, we see allergy patients every day, yet we might not always reflect much on the allergic response and why this process is relevant to the care we deliver and the recommendations we make. However, being mindful of the allergic cascade is central to how allergy in general, and itching in particular are best managed.

First, keep in mind that an allergy is actually a defense mechanism. It's our body's way of fighting off things like ragweed and grass. But this battle involves a series of chain of reactions that lead to the release of chemical mediators, including histamine. Histamine is one of the chemical granules inside a mast cell. When the mast cell is tagged by an antibody, it essentially begins to explode and blow apart. This happens quickly and these histamine granules are very irritating once they've been released. Systemically, they lead to itching and sneezing and, in the eye, they cause significant patient irritation and discomfort. Of course, histamine can be combated using antihistamines, steroids and some mast cell stabilizers, but because it's released so quickly following exposure, management can be a challenge. An awareness of this helps us appreciate why it's so important to stabilize the mast cell to control allergy as well as blunt the response to re-

HISTAMINE AND THE ALLERGIC RESPONSE

In seasonal and perennial allergies, allergens, such as grass or ragweed pollen, dust mites, and animal dander, can cause an immune reaction mediated by immunoglobulin E (IgE).[13] A cascade of events leads to mast-cell degranulation and release of histamine and other proinflammatory mediators at the site of allergen invasion.[13] The inflammatory reaction results in vasodilation, increased vascular permeability, leukocyte chemotaxis, and emigration of inflammatory cells into the surrounding tissues spaces, causing signs and symptoms of inflammation.[13]

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Table 1: Comparison of key characteristics of nasal, oral, and ophthalmic anti-allergy over-the-counter medications.

	Nasal	Oral	Ophthamic			
Drug Class	Steroid	Antihistamine	Lubricant or Astringent*	Antihistamine + Vasoconstrictor	Antihistamine + Mast Cell Stabilizer	
Example Brand(s)	Flonase Allergy Relief	Claritin Tablets	Clear Eyes Dry & Itchy Relief, Visine A.C. Itchy Relief	Visine Allergy Eye Relief Mulit-Action	Alaway	Pataday Once Daily Relief Extra Strength
Example Active Ingredients	Fluticasone propionate (glucocorticold) 50 mcg	Loratadine 10 mg	Glycerin 0.25% Zinc Sulfate 0.25%	Naphazoline HCl 0.025%, Pheniramine maleate 0.3%	Ketotifen 0.025%	Olopatadine 0.7%
Onset of Action	Full effect may take up to several days	Within 1-3 hrs, maximum effect 8-12 hrs	Itch data not reported	Within minutes	Within minutes	Within minutes
Duration of Action	24 hours	24 hours	Itch data not reported	6 hours	12 hours	24 hours
pH					4.4-6.0	6-7

* Not approved as anti-allergy drops

leased histamine. Indeed, there is significant value in treating it from both sides with dual mechanisms of action.

THE PATIENT EXPERIENCE

Many allergy sufferers endure chronic discomfort, yet they often keep their ocular complaints to themselves until they reach a more acute stage, which is when they commonly present in specialty practices. Remarkably, only 10% of patients with ocular allergy symptoms seek any professional care.[4] By the time they decide to seek care, many of these patients have ocular inflammation, itching, redness, tearing, chemosis, and eyelid swelling. This is why it's so important that health providers in all specialties ask about ocular symptoms. Patients truly are suffering in silence.

People with chronic disease are used to feeling uncomfortable and don't know any other way. It becomes normal. It's the clinician's responsibility to be proactive and look for signs and ask questions about ocular symptoms specifically. We also need to keep in mind that, before they come to see us, many patients are buying over-the-counter (OTC) oral non-sedating antihistamines and intranasal corticosteroids.[5] Some select treatment more or less at random, without talking to a pharmacist or their health care provider. The self-diagnosis and management can result in dissatisfaction with these treatments.[5] Complaints include incomplete relief, slow onset of relief, short duration of relief and reduced efficacy over time.[5] Eventually these patients discontinue use or change medications, with most citing inadequate efficacy as the primary cause.[5]

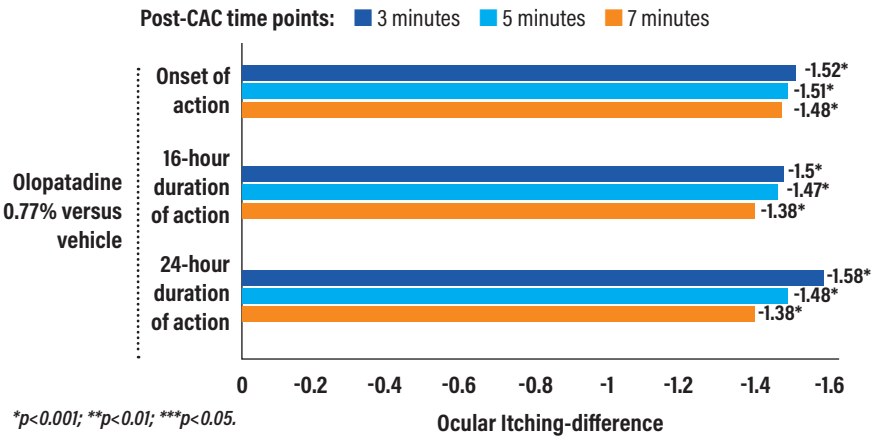
Many patients think that drugs that are approved for eye allergy itch relief all have the same efficacy on the eye. We need to re-educate patients and help them understand how allergies, and the medications they choose to treat them, will affect their entire system. Many patients who have tried oral and nasal medications and still experience itch, watery eyes and redness. Some have also tried drops that claim to provide itch relief, but that lack an antihistamine, which we know is so instrumental in combatting common allergens.

TREATMENT CATEGORIES

When we are advising patients who are suffering with itchy eyes due to allergic conjunctivitis, we have three main categories of medications for eye itch relief—over-the-counter oral, nasal, and ophthalmic medications. However, there are the key differences between

OLOPATADINE 0.77% RELIEVES EYE ALLERGY ITCH FASTER AND BETTER THAN PLACEBO CONTROL FOR A FULL 24 HOURS

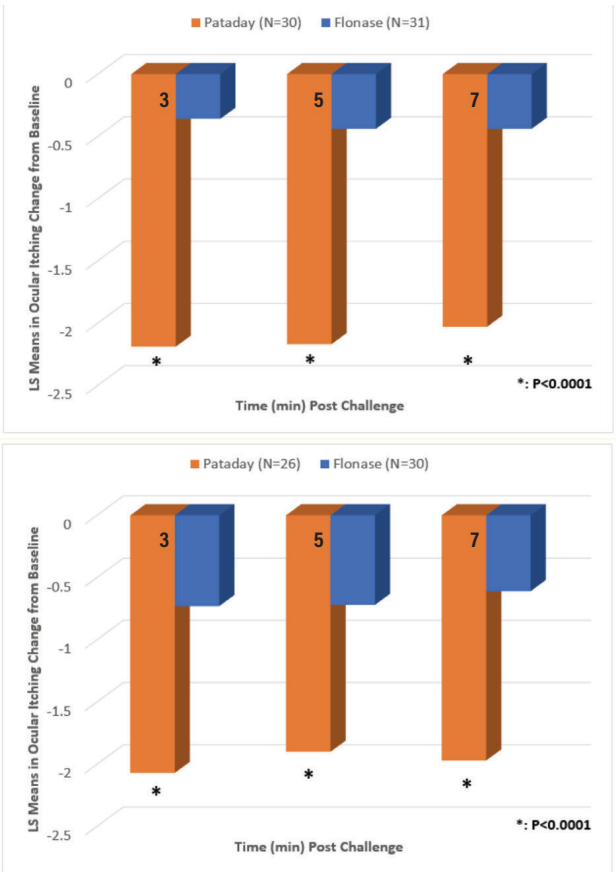
A Phase III, multi-center, double-masked, parallel group, randomized clinical trial compared the safety and efficacy of Pataday Extra Strength against vehicle using a conjunctival allergen challenge (CAC) model.[13] Following the conjunctival allergen challenge, the patient was given either vehicle or Pataday Extra Strength. Onset of action and duration of action were both assessed. As the figure illustrates, Pataday Extra Strength relieved ocular allergy itch faster and better at all measured times and was effective for 24 hours. This strong clinical evidence should give providers confidence in recommending this for their patients who do not like frequent dosing and want long-lasting relief.



Treatment differences in means after conjunctival allergen challenge (CAC): primary endpoint of ocular itching at 27 minutes (onset), 16-hours, and 24- hours post-dose administration.[13]

OLOPATADINE 0.77% VERSUS STEROID NASAL SPRAY

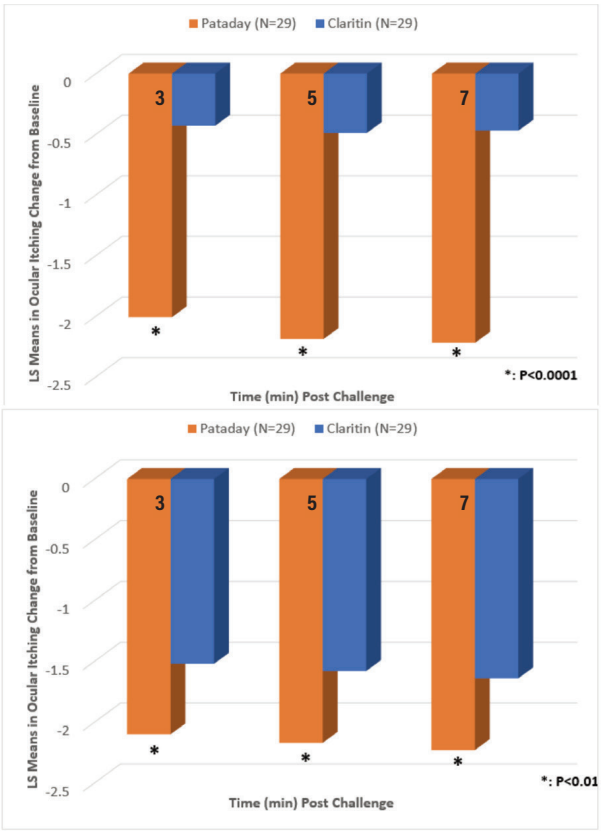
A randomized, double-masked, parallel study compared the efficacy of Pataday Once Daily Relief Extra Strength to Flonase Allergy Relief, which is a nasal steroid spray approved for relieving multiple symptoms of hay fever, including itchy eyes.[14] Participants were treated with either Pataday (n = 30) or Flonase (n = 31), and then 15 minutes later were exposed to allergen drops to trigger an allergic response. At 3, 5, and 7 minutes after allergen exposure, participants in the Pataday group reported significantly lower eye itch scores compared to those in the Flonase study group. After 2 weeks of treatment, the Pataday group continued to report significantly lower eye allergy itch scores compared to those in the Flonase group 24 hours after treatment at all measured time points.



At onset (top) and 24 hours (bottom) after treatment, mean eye itching scores were significantly lower in the Pataday® Once Daily Relief Extra Strength group compared to the Flonase® Allergy Relief group.[14]

OLOPATADINE 0.77% VERSUS ORAL ANTIHISTAMINE

In a recent study, Pataday Once Daily Relief Extra Strength (n = 29) was compared to Claritin 24-hour tablets (n = 29), which is an oral antihistamine approved for relieving multiple symptoms of hay fever, including itchy eyes.[15] Participants in the Pataday group reported significantly lower eye allergy itch scores compared to those in the Claritin study group approximately 15 minutes after treatment. And, as with the nasal spray study, eye allergy itch assessments were also conducted 2 weeks after self-treating at home. Participants in the Pataday group reported statistically significantly lower itch scores compared to those in the Claritin group 24 hours after treatment. This is important because patients often think they can take one medication and it will treat all of their different symptoms, so understanding how this compares is particularly important.



At 15 minutes (top) and 24 hours (bottom) after treatment, mean eye itching scores were significantly (P<0.0001) lower in the Pataday® Once Daily Relief Extra Strength group compared to the Claritin® Tablets 24-Hour group.[15]

these medications (*Table 1*).

With regard to nasal steroid sprays, steroids have anti-inflammatory activity and are very effective in relieving symptoms of nasal congestion and have been shown to relieve symptoms of itchy, watery eyes. However, it can take several days of regular use to achieve the full effect and is associated with side effects that should be considered before use.[6]

With regard to oral antihistamines for treatment for ocular itching, the first consideration is that they need to be absorbed and make their way through the body. However, it can take up to 1-3 hours to begin working to reduce symptoms of itch and as many as 8-12 hours to reach maximum effect.[7]

A third treatment category includes eye drops. On one hand, we're very fortunate to be able to put medicine directly on the target organ, but we must be cognizant of the fact that not all topicals are created equal. There is a lot of diversity in this category and it can be very confusing for patients due to how some of these medications are marketed. For example, some drops are marketed for "itchy" eyes but do not contain active agents that target mast cells or histamine receptors. Examples of these products include CLEAR EYES Dry and Itchy Relief[8] and VISINE A.C. Itchy Eye Relief.[9] These products are classified as lubricants and astringents, respectively, and do not contain steroids, antihistamines, or mast cell stabilizers. Rather, they are indicated for the temporary relief of discomfort due to minor eye irritations and not specifically for eye itch due to hay fever or environmental allergens.

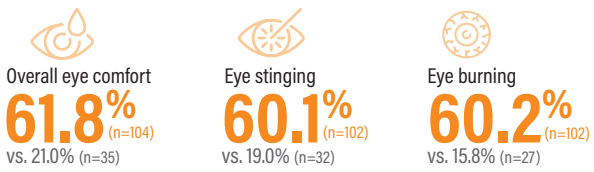
If we're looking at lubricants and astringents as a subcategory of the topical ophthalmics, another subcategory would be the combination antihistamine and vasoconstrictors. This group of medications includes drops such as Visine Allergy Eye Relief Multi-Action.[10]

OLOPATADINE 0.77% VERSUS OTHER OPHTHALMIC ANTIHISTAMINES

With topicals, tolerance is extremely important. You want a drop that offers relief with minimal irritation upon instillation. In two separate prospective, randomized, single-masked, contralateral, single-site clinical studies, comfort upon application of Pataday Once Daily Relief Extra Strength was compared to Visine Allergy Eye Relief and the other with Alaway.[16,17] The Pataday group reported significantly higher comfort scores compared to the Visine Allergy group immediately upon drop application, and at 30 seconds, 1 and 2 minutes after application and to the Alaway group immediately upon drop application, and at 30 seconds, 1 and 2 minutes after application. Furthermore, approximately 3 times more participants reported that they either preferred or strongly preferred Pataday Extra Strength over Visine Allergy based on overall comfort and symptoms of stinging and over Alaway based on overall comfort and symptoms of stinging, burning, and foreign body sensation.

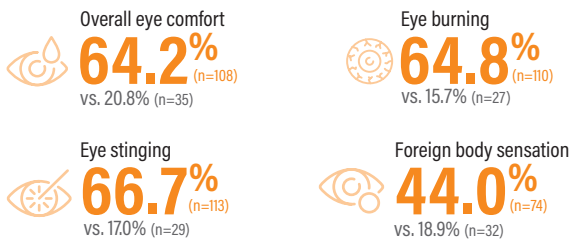
Approximately 3-times more participants preferred Pataday over Visine based on overall comfort and stinging.

Percentage of participants who reported preference or strong preference for Pataday vs. Visine Allergy:



At least 3-times more participants preferred Pataday over Alaway based on comfort, burning, and stinging

Percentage of participants who reported preference or strong preference for Pataday vs. Alaway:



These drops are indicated for allergy itch relief, but they require dosing 4 times daily, which can be burdensome and can result in rebound redness upon discontinuation. Another factor to consider is that some drops are more acidic than the natural pH of the tear film, so patients might experience mild irritation upon application. The pH of the average human tear film is close to 7.0, but Alaway with ketotifen has a pH of 4.6 to 6.0.[11]

The other drop in this category is Pataday Once Daily Extra Strength with olopatadine 0.7%. This is a dual action agent that stabilizes mast cells and blocks histamine receptors. Unlike Alaway, its effects last a full 24 hours, requiring only once daily dosing. Furthermore, the pH of Pataday Once Daily Extra Strength is 6.0. to 7.0,[12] which is similar to that of the normal human ocular surface tear film.

ONCE-A-DAY DOSING WITH OLOPATADINE 0.7%

Pataday Once Daily Relief Extra Strength is indicated for temporarily relieving itchy eyes caused by allergens, including pollen, ragweed, grass, and animal dander and hair. It is approved to be used once a day in adults and children 2 years and older and provides effects that last up to 24 hours. Since it's topical, it hits the target cells right away. It hits right away and it blocks any histamine receptors that haven't been yet sensitized. Pataday Once Daily Relief Extra Strength offers an ideal combination of benefits and can give patients something that works fast and is long-lasting.

Along with having 0.7% olopatadine, its pH reduces stinging and burning with instillation, making it very comfortable for patients. Furthermore, an effective once-a-day drop also makes it extremely convenient for patients. For example, patients who wear contact lenses don't have to take their lenses out several times during the day to redose. It's an enormous difference for patients when they can use a medication once a day and continue to have a benefit, whether it's so they can work a long day or simply not wake up the next day with symptoms. They're covered for 24 hours with Pataday Extra Strength Once Daily Relief.

HELP PATIENTS NAVIGATE OPTIONS

In summary, there are many options for itchy allergy eyes. It's complex for specialists to navigate, so imagine how overwhelming it can be for patients as they try to select among the many OTC options at a pharmacy. It's confusing, but a little guidance from us can go a long way and can help save patients the frustration of trying different types of treatments until they find one that meets their needs. As clinicians, we are armed with clinical evidence to better advise our patients.

With respect to Pataday Extra Strength, it has been shown to relieve eye allergy itch faster and significantly greater at 24 hours compared to both Claritin Tablets and Flonase Allergy. It has also been shown to be more comfortable upon application compared to Alaway and Visine Allergy Relief. Therefore, Pataday Extra Strength is a very strong option for patients with eye allergy itch who are seeking a comfortable eye drop that provides fast relief that can last up to 24 hours with just a single drop. ■

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ing as well as it did beforehand. But if I'm hoping to elevate the pressure a little bit, I don't want that trabeculectomy to work as well. In that scenario, I might use considerably fewer postop topical steroids, or in some cases, maybe no steroids at all, because I'm just hoping to harness some of that intraocular inflammation to promote that subconjunctival fibrosis scarring. I think that'd be the easiest thing when you're just looking for a little bit of an increase in IOP."

Although not a new technique, Dr. Boese suggests an autologous blood patch as an option. "I think it's something that deserves a little bit more credit because it's not very invasive and it's a technique that can help in some patients," she says. "The blood patch can be a good tool when you have reasonable expectations and only when you're trying to move the pressure up by just a couple points. It's not going to be your tool if you're looking to get that pressure up significantly. One of the nice things is it can be done safely in the clinic. You don't have to take the patient to the OR."

However, cataract surgeons may not be as familiar with the technique as glaucoma surgeons. Dr. Boese says it helps to have a second person there who draws up a little of the patient's blood from the antecubital vein and gives that syringe to the surgeon.

"You quickly put in a small needle, usually a 30-gauge is just fine, and then you go into the bleb itself," she says. "You want to start peripherally where the conjunctiva is more healthy. Go into the bleb itself, unlike needling where you're actually sweeping and breaking up some of those loculations, you actually would just want to gently pierce into these loculations and inject a small amount of blood. You end up seeing these patchy pockets of blood overlying the flap as well as in that overfiltering subconjunctival space. The idea is that blood itself is inflammatory, so by putting blood in this space, you're trying to promote subconjunctival fibrosis. It doesn't work for everybody, but it only takes a few minutes and in some cases, it's all they need.

"Of course afterwards, you're not going to be putting them on steroids because the whole idea is letting that inflammation help you out," continues Dr. Boese. "I think it's an underutilized tool and a nice thing to pull out when you're trying to see if something in clinic might be enough."

• ***Treatment in patients with bleb dysesthesia.*** Dr. Piltz-Seymour says the first step for bleb dysesthesia is conservative, with lubricants and ointments to help smooth the ocular surface. If the issue resolves itself after that treatment, she would proceed with cataract surgery. "However, if dysesthesia persists, anything you can do to flatten out the contour of the bleb is beneficial," she says. "I typically place external compression sutures, that's usually our best bet. Others also recommend using techniques like using trichloroacetic acid or painting the bleb with Rose Bengal and using laser or using cautery. I've tried these techniques, but haven't found them as helpful as external compression sutures. If the compression sutures don't do the trick, I do a bleb revision, excising the bulk of the old bleb and pulling down fresh conjunctiva."

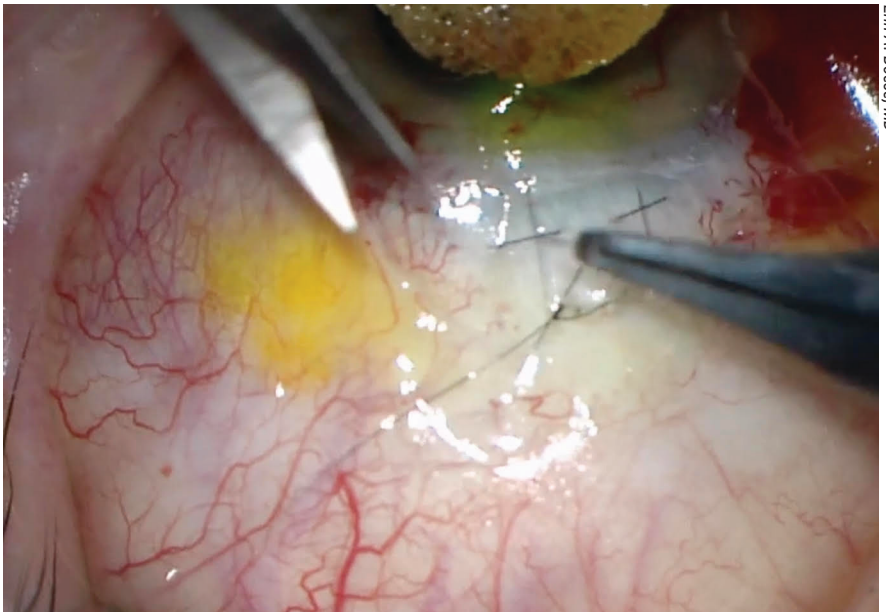
• ***Treatment with hypotony.*** If the patient requires a significant boost in IOP, Dr. Boese recommends a surgical revision. "This is the most effective way to increase the IOP, even though it means an extra trip to the OR," she says. "A surgical revision involves replacing the nylon sutures in the scleral flap as a way to decrease the flow through the trabeculectomy flap."

Dr. Boese cautions that this addresses the root cause of the problem, but could unintentionally spike the patient's pressure too high. "Surgeons have to be prepared and think multiple steps ahead," she says.

For the severe cases involving hypotony maculopathy or macular striae, Dr. Piltz-Seymour has several considerations. "During cataract surgery, my first recommendation is to place transconjunctival sutures through the scleral flap to try to close down some of the flow through the trabeculectomy flap," she says. "Many people think the bleb filters in all areas along the scleral flap, but when a trabeculectomy develops, there's typically only a very localized place on the scleral flap that drains—a small localized fistula—so you need to find out where that spot is in order to put your sutures. I recommend injecting trypan blue into the anterior chamber and then, as the stained aqueous drains from the flap, it will mark the location of the localized fistula. You only need to place transconjunctival sutures in this location. You can place a couple of sutures and that'll usually help to raise the pressure."

If that doesn't work, she creates a limbus-based conjunctival flap by incising the conjunctiva posterior to the bleb in the fornix. "Reflect the bleb over the cornea and then try to reinforce the flap either with additional interrupted sutures, mattress sutures or by securing graft material over the flap to tamponade it with mattress sutures," says Dr. Piltz-Seymour. "I want to stress that if you need to place a graft, use mattress sutures over the graft to put pressure on the bleb; interrupted sutures around the edge of the flap are less useful. And trypan blue again can help to identify the exact area of overfiltration."

She emphasizes that, in the presence of macular striae, you really need a definitive approach to raising the IOP. "We sometimes like to elevate the pressure into the 20s for a short time to flatten out that macula and then have a plan to lower the IOP back to the target level," Dr. Piltz-Seymour says. "When securing the scleral flap either with transcon-



Erin A. Boese, MD

Performing a surgical revision of the bleb is a good way to proceed if you need a significant increase in IOP to avoid the consequences of doing cataract surgery on a hypotonous eye. This should be done prior to the cataract surgery to ensure that optical measurements are made with the eye at a normal pressure.

junctival sutures or an open technique, it's advisable to place two sets of sutures, tight ones to initially raise the IOP into the low 20s that can be released, and looser ones to stay long term. If using graft material over the flap, the tight sutures will need to be releasable sutures. In reality, it may not be that easy to titrate the IOP with tighter and looser sutures, especially when placed transconjunctivally, since the actual fistula is so localized. Usually, what I recommend is to take out the cataract, place the transconjunctival sutures and if I don't get the result that I want, plan to do an open approach."

Finally, as a last resort, you can excise the old bleb, secure the flap as described above, and bring fresh conjunctiva down, Dr. Piltz-Seymour continues.

IOL Calc Considerations

Hypotony can impact IOL calculations and in extreme cases should be addressed prior to taking those measurements, say both surgeons.

"A hypotonous eye becomes shorter, and if the hypotony reverses, the eye expands, but not usually to the full baseline axial length," says Dr. Piltz-Seymour. "Whether you performed biometry measurements before the hypotony developed or after, there will be issues with IOL accuracy."

Dr. Boese says calculations may not be thrown off too much if the pressure only needs to come up slightly, but it still influences her target. "If I'm planning to do cataract surgery along with a glaucoma surgery and I'm planning to lower the pressure I might choose a slightly more myopic target because I know that eye might be a little bit shorter," she says. "The opposite might be true for when I'm purposely trying to increase the axial length and increase the eye pressure. I might end up picking a target closer to plano or even slightly hyperopic if I'm really pretty certain that I can get that axial length a little bit longer. I think in general, a lot of us prefer to be slightly myopic than slightly hyperopic, so I just might not need to aim quite so myopic with my calculations."

Astigmatism is another factor to consider. "One thing to be wary of is when that pressure is low, not only will your axial length be changed and your IOL calcs be different, but it can also trick you into thinking that there's a lot more astigmatism in the eye than there actually is," Dr. Boese continues. "The eye actually can have pretty significant regular with-the-rule astigmatism just because the eye is sinking in on itself a little bit. If you were to look at that out of context, you might say, 'Well, gosh, I might put a toric lens in this person,' and actually end up inducing astigmatism when the pressure goes up."

Similarly, if additional flap sutures are going to be placed, changes in astigmatism can develop, adds Dr. Piltz-Seymour. "Patients need to be warned that there may be a need for glasses if the adjusted measurements aren't right on the mark. Most of these patients won't be multifocal candidates so postoperative vision can be corrected with glasses if needed."

In order to achieve optimal outcomes, Dr. Boese says preop planning is going to be your best friend.

"Not only are there all of those impacts on the IOL calculations, but you also want to make sure you're setting patient expectations appropriately," she says. "Hypotony can be hard to fix. It's so much easier for us to lower a high pressure than to raise a really low one. Have realistic expectations of what you can expect with each of these tools, and also decide whether or not you want to address the hypotony and cataract in a staged approach. Cataracts can usually wait. If delaying the cataract surgery with a staged approach works better and it puts you in a better position for good outcomes, I don't think anyone would fault you for that." ◀

DISCLOSURES

Dr. Boese reports no financial disclosures. **Dr. Piltz-Seymour** is a consultant and speaker for Aerie Pharmaceuticals and Alcon; and consultant for Nanoscope Therapeutics.

DMEK Rebubbling At the Slit Lamp

If you don't have easy access to the operating room, rebubbling at the slit lamp offers flexibility. Here's my approach.

SUMIT (SAM) GARG, MD
IRVINE, CALIF.

Descemet's membrane endothelial keratoplasty is the gold standard for the surgical treatment of corneal endothelial disorders, offering fast visual recovery, good visual outcomes and low graft rejection rates.[1,2] The most frequent postoperative complication of DMEK is partial graft detachment.[3] It's commonly addressed by rebubbling with air or 20% sulfur hexafluoride.

Risk factors for rebubbling may include older recipient age and surgical complications;[4,5] however, findings in the literature have been mixed, with some studies reporting that donor characteristics; graft preservation, preparation and cell count; and recipient lens status have no effect with regard to rebubble rates.[6,7]

Rebubbling can be performed in the operating room or at the slit lamp. I've found that rebubbling at the slit lamp is a good alternative approach to the OR that can be incorporated into the clinic day without throwing a wrench in my schedule. If OR access is limited,[8] the slit lamp provides flexibility. Here, I'll describe my technique.

When to Rebubble

Fortunately, DMEK rebubbling rates are low, especially with the primary use of 20% SF6 gas at the time of surgery. I generally have a low threshold for rebubbling if a patient's vision isn't recovering as it should. Though minor DMEK detachments will often reattach on their own if given enough time, the patient's vision may suffer during that period. Bullae or haze may develop if there's significant corneal edema over a period of time.

I consider rebubbling if more than 30 percent of the graft area is separated from the posterior cornea, especially if it's in the center of the visual axis; if the patient's vision isn't improving as expected; and if there's curling of the graft and/or progressive separation from the posterior cornea.

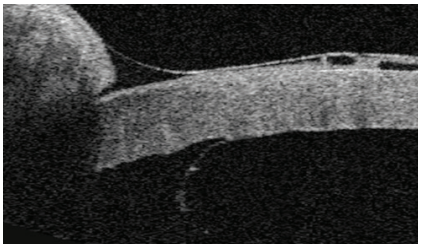


Figure 1. An incorrectly oriented graft.

Graft Orientation

When assessing a detachment, first ensure the graft orientation is correct, with the endothelium down and the orientation marker, such as an "S" or "F" stamp, facing the correct way. Anterior segment optical coherence tomography is helpful for evaluating detached grafts and for determining whether the graft is curving in the proper direction or not (*Figure 1*). In my practice, we use AS-OCT to find areas of detachment that may otherwise not be fully apparent at the slit lamp (*Figures 2-3*).

The Setup

After obtaining informed consent from the patient, ensuring they

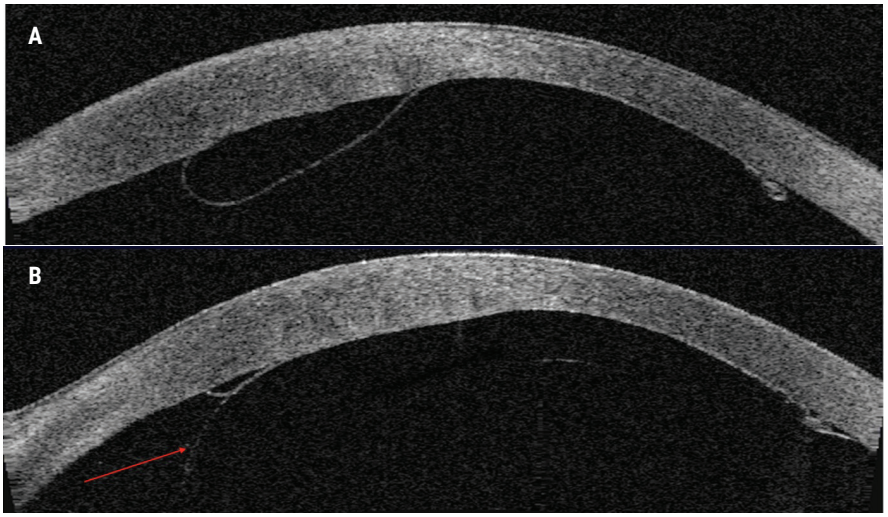


Figure 2. A partial detachment in a correctly oriented graft (A). The graft reattaches inferiorly after injection of a gas bubble (red arrow) (B).

This article has no commercial sponsorship.

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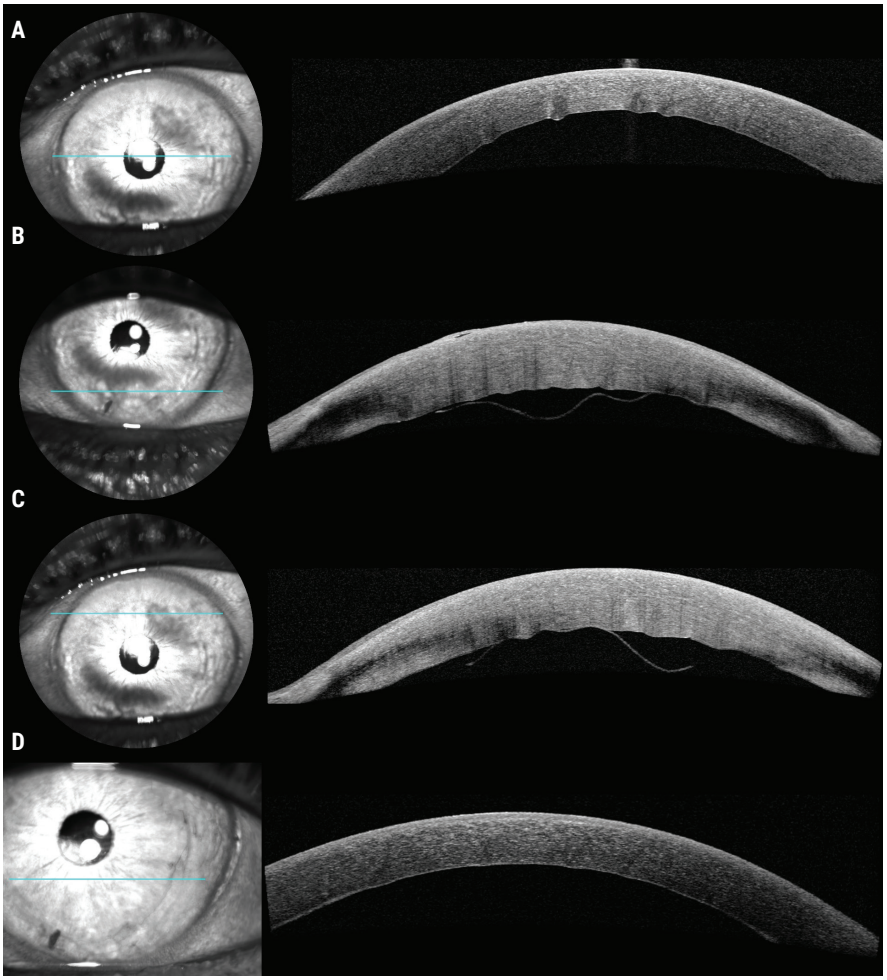

Figure 3. A diffuse detachment with good central apposition to the posterior stroma (A) but inferior and superior detachment and corresponding thickening of the overlying cornea (B, C). After rebubbling, the graft shows good apposition against the posterior cornea as well as stromal thinning (D).

understand what's going to happen and why, as well as their alternatives, check to make sure all of your tools and equipment are set up. These include topical anesthesia, Betadine, a speculum, two 30-gauge cannulas, two 3-cc syringes, balanced salt solution and topical antibiotics (moxifloxacin).

Check to make sure the patient is comfortable in the slit lamp, and also be mindful of your own comfort. This is a one-handed technique with some assistance from your second hand, so a comfortable hand position with the slit lamp aperture out of the way and good visualization are key. Having something under your elbow to support may help, though there is some free-floating involved. It's not the most comfortable procedure by any means but it becomes much more efficient to perform in the clinic than having to go to the operating room. Usual sterile precautions are followed.

The Procedure

A DMEK rebubbling procedure at the slit lamp takes about three to five minutes. The final outcome in terms of endothelial cell count is often equivalent to that of eyes that didn't require rebubbling (*Figure 4*). Here's my approach:

Place the topical anesthesia and then place the speculum. To ensure I've cleaned adequately, I like to do a limited Betadine prep and some topical antibiotics within the eye. Then, I prepare my cannulas: one with air and one with BSS.

One key step is releasing some aqueous from the anterior chamber by gently depressing the lip of your paracentesis wound with the 30g cannula. You want to create space to place your air fill. Often, surgeons will inject without releasing any fluid from the eye, and that causes the IOP to spike.

Insert the cannula. When you insert the cannula after releasing some aqueous, ensure the cannula is anterior to the iris and posterior to the graft. This may sound obvious, but sometimes when the visualization is poor it can be hard to determine where the cannula is in relation to the DMEK graft. If you're not sure, don't inject. Check that the patient is looking straight ahead.

Inject air behind the graft until the bubble fills the chamber. I usually inject air from below, even if I have a superior paracentesis, for two reasons: one, it's ergonomically easier, and two, there's less air loss as you're injecting. If you go superiorly, sometimes the injected air comes right back out. If you go from below, the air tends to stay in the eye better. If necessary, release some pressure from an existing paracentesis superiorly. (If you don't have a 30-gauge cannula, a 30-gauge needle will work. Create a fresh incision using the needle, go inferiorly and inject through the needle.)

When you inject, inject slowly. Very commonly surgeons will inject with a quick burst of air. When the patient isn't anesthetized with a block or is on the table or in a setup where they could move, that quick influx of air may make the patient jump. Aim for a nice, easy fill over a few seconds. You can generally see the graft reattach to the posterior cornea as you do that.

Once you're done, confirm the patient's vision. Rebubbling can lead to very high pressures in the eye. If the pressure goes up significantly it can overcome the circulation in the back of the eye. Be sure the patient can see at least hand motion.

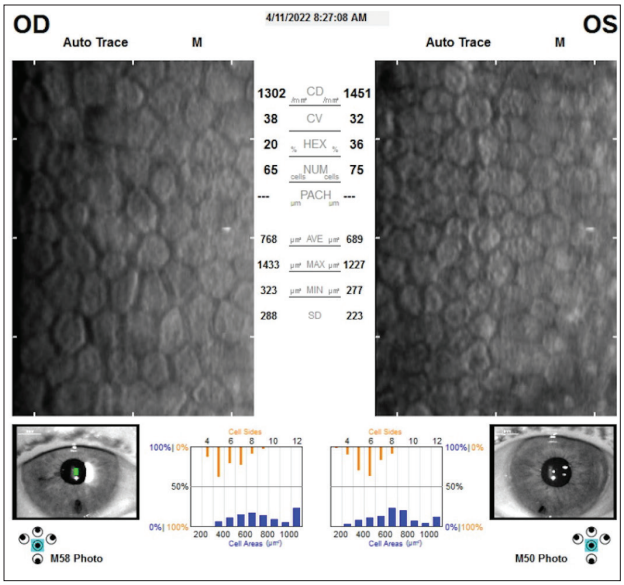

Figure 4. Comparison of the right and left eyes of a patient who underwent bilateral DMEK. Only the left eye required rebubbling. Specular microscopy shows little to no difference between the appearance of each eye's endothelial cells.

Finally, place the topical antibiotic. I usually leave patients supine for 10 to 15 minutes to give the graft time to adhere and then check the patients' pressures.

In conclusion, if you do DMEK, knowing how to rebubble is key. Performing this procedure for partial graft detachments at the slit lamp is a convenient alternative to the OR, and one that's often easier on the patient.

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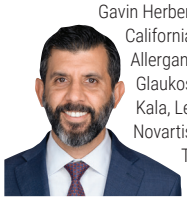

There But for the Grace of God

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

As physicians, we tend to see people in less-than-their-best moments. Aside from our "well vision" exams, most of our patients come to us with a problem or, in so many cases, lots of problems—many eye problems, many medical problems, and not infrequently psychosocial ones as well. I guess it sort of depends on where and what type of practice you have.

In my urban setting, it's quite a cross-section, with a very definite emphasis on the elderly and infirm. Diagnosing and fixing their eye issues is mostly an easy chore. Wrangling their other issues—not so simple. Most of us have seen more than our fair share of diabetic retinopathy in patients who refuse or are simply unable to control their blood sugar. We spend a lot of time staying up to date on best practices for treating PDR/DME; we know what to do, what works and what doesn't. How do we make our efforts bear fruit if we can't also get the patient to do better with their blood sugar or even come into the office? We can't ignore the non-ophthalmic components of our patients' lives that impact their response to health-care interventions. It's even more challenging in the very elderly group, especially those with poor or absent support systems.

As the population grows older, we're seeing an increasing number who are alone or almost alone and many with varying degrees of cognitive dysfunction. How do they survive in a complex society?

Getty

How do they deal with their health insurance, their pharmacy benefits, transportation, appointments and home care? I find it tough at times to manage all those and can't fathom how an 85-year-old by themselves can. Think of the patients who can't administer their glaucoma drops hitting their eye perfectly with one drop so they don't run out of meds before the month is over, or the cataract patient who needs preop clearance from a cardiologist who's booked up for six months, so their cataract surgery will have to wait. A six-month delay is a large percentage of some people's remaining lifespan. You or I would be able to wrangle an appointment, but who advocates for these individuals?

Just this week I entered my office to see preop cataract patients and among the eagerly waiting there were two very elderly, frail, dishevelled women, one with her walker. That was my patient, the other her sister. They lived together and had no other friends or family. They came in because the one couldn't see well and they wanted her eyes checked for cataracts. Her vision was CF and 20/400. She was the driver … and still driving. I told them that we could do surgery to hopefully get back useful vision so that she could potentially drive again. I was also struggling to imagine how her arthritic legs and back would allow her to manage the pedals and the steering wheel even with good vision. I also had to tell them that she couldn't drive in her current condition. They were distraught. They had no other way to shop for food or other essentials.

As my staff started to reach out to the social worker to try to help them with a solution, I was reminded how perilous their lives were. With all its warts, we have created an amazing health-care ecosystem. What we haven't done is have a structure that ensures everyone can access it. Yes, finances are a big factor, but the simple ergonomics escape so many. I reflected on how fortunate I was to have my health, and a strong social network of family and friends. But for how long? Eventually, the end comes for all of us. Not having to face it sick and alone is a gift from above. We are at times reminded that not everyone is so lucky. ◀

This article has no commercial sponsorship. **Dr. Blecher** is an attending surgeon at Wills Eye Hospital.

LIGHT ADJUSTABLE LENS: PRACTICE INTEGRATION

Is the LAL right for your practice?
Experts share how they navigated the adjustable waters of this new technology.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

The Light Adjustable Lens (RxSight) has been in clinics around the country for a few years now, following its FDA approval in late 2017. Many surgeons have touted the advanced-technology lens for its ability to accept lens power modifications after implantation. The three-piece monofocal lens is implanted like any other monofocal, making the surgical aspect simple to adopt.

The company, RxSight, is still innovating. First-generation lenses required patients to wear UV eye protection at all times before the final lock-in treatments. Vance Thompson, MD, of Vance Thompson Vision in Sioux Falls, South Dakota, who was an investigator in the LAL's FDA monitored trials, says that patients no longer need to wear UV protection while indoors because of the LAL's new ActivShield technology, which prevents ambient UV light from tampering with the lens power before or between adjustments and lock-ins. He notes that "in theory, patients shouldn't have to wear UV-protection goggles when outdoors but for now we've been recommending they do until their final lock-in." He adds that this advancement has helped to increase doctor and patient comfort.

As you know, with adjustments and lock-ins, the LAL requires more work than most other IOLs. Amir Marvasti, MD, of Coastal Vision Medical Group in Orange County, California, compares the LAL practice experience to a combination of cataract surgery, general ophthalmology and LASIK. "The LAL experience for the surgeon feels similar to the situation of a presbyopic patient with a low prescription who needs two or three LASIK treatments to get them to the finish line," he says. "The refraction and dilation feel like the preop process of LASIK, and patients expect a LASIK-like outcome."

From LASIK-like preop testing and refractions to purchasing new technology and accommodating additional postops for adjustments and lock-ins, the process is involved. Elizabeth Yeu, MD, of Virginia Eye Consultants in Norfolk says the LAL is an exciting technology but one that wasn't the best fit for the flow of her current practice. "With careful preop testing, we can achieve very precise results in a majority of our patients. I definitely see the benefits of LAL, especially for tweaking monovision outcomes and for post-refractive surgery surprises. But, in my current clinical practice, the multiple postoperative visits are a little complicated to manage for both the patients and our referring ODs," she says. "I do think that some form of adjustable IOLs is the future if the lenses could be indefinitely tweaked or if the platform could be changed from say, monofocal to an EDOF."

Whether they choose to offer the LAL or not, physicians agree that the LAL is an exciting addition to the cataract surgeon's toolbox and one that heralds a new wave of adjustable technology—but questions may remain. What do these additional postop visits look like? What

This article has no commercial sponsorship.

Dr. Thompson is a consultant and researcher for RxSight. Dr. Vukich is a consultant for RxSight and has been an investigator for RxSight in the past. **Dr. Mamalis** is on the Perfect Lens advisory board. **Drs. Yeu**, **Lee** and **Marvasti** report no related financial disclosures.

MANY MANIFESTATIONS OF THYROID EYE DISEASE (TED)

ONE ROOT CAUSE[1-3]

TEPEZZA®
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Treat TED at the source[1,4-6]

TEPEZZA is the **first and only FDA-approved** treatment specifically for TED[1,4]

TEPEZZA has been shown to be effective in patients with a **wide range of clinical manifestations**[5-7]

TEPEZZA **alleviates many of the symptoms of TED** by producing anatomic changes to the tissues behind the eye[1,4,7-10]

TEPEZZA treats the root cause of TED and has been proven to:

- Decrease proptosis[4]
- Improve diplopia[4]
- Reduce orbital pain, redness, and swelling[7,11]
- Improve functional vision and patient appearance[7,11]

... in patients with TED, without concomitant steroids (vs placebo at Week 24) in 2 clinical studies.[7,11,12]

See how TEPEZZA can transform your patients' eyes

IGF-1R, insulin-like growth factor-1 receptor.

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INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary. Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, dry skin, weight decreased, nail disorders, and menstrual disorders.

Please see Full Prescribing Information or visit TEPEZZAhcp.com for more information.

TEPEZZA®
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or preexisting diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions]*
- Exacerbation of Preexisting Inflammatory Bowel Disease *[see Warnings and Precautions]*
- Hyperglycemia *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84, N(%)	Placebo N=84, N(%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder[d]	4 (5%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)
d - Nail disorder (includes nail discoloration, nail disorder, and onychoclasis)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders: diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Preexisting Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control measures including medications as appropriate. Encourage compliance with glycemic control.

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type of scheduling works best? How will this affect clinic volume? Is it worth it? Here, several cataract surgeons discuss their experiences incorporating the Light Adjustable Lens into their practices and share the adjustable technologies in the pipeline they're looking forward to.

Patient Education

Some surgeons say they enjoy the simplicity of the preoperative discussion about lens selection and refractive outcome with the LAL since the lens's customizable nature removes some of the burden of lens choice with regard to sacrificing visual quality for increased visual range.

"With multifocals, we spend a significant amount of time explaining lens technologies to patients, deciding who will like what type of lens (knowing there are positives and negatives to each one) or who will do well with a mix-and-match strategy," says John Vukich, MD, of Summit Eye Care of Wisconsin in Wauwatosa. "Multifocal lenses require giving up something and the unhappy patients are truly a challenge."

Dr. Vukich says he's had far fewer unhappy patients since he began implanting the LAL. He frequently offers LAL patients a blended-vision strategy. "Patients can try it on for size so you don't have to choose what you think they might like," he says. "Let them live with it for a while and then perform the adjustments based on their feedback. It becomes an iterative process in which the patient is a participant. That adds a great deal of not only satisfaction but patient confidence in the process."

While the initial conversation about choice of lens may be simpler in some ways, there are still adjustment decisions to be made after the surgery. "Some patients have trouble making up their minds about their goal or target, and that can cause delays in the light adjustment treatments," points out Bryan S. Lee, MD, JD, of Altos Eye Physicians in Los Altos, California. "Other times, we need to treat dry eye to get a cleaner refraction. It's a good idea to have your team on the same page so everyone understands that there's some flexibility needed with these patients. You might have to push things back by another week."

> **When we start talking about the LAL's LASIK-like accuracy, patients almost hear the word 'perfect.' That's why it's so important to set up expectations.**
>
> ***— Vance Thompson, MD***

As with any lens, but particularly with a premium lens marketed as "customizable," setting patient expectations with thorough education and "underselling" can help guard against unhappiness. "I like patients to understand the variables of lens implant healing after cataract surgery and how that can affect their vision," Dr. Thompson says. "I explain to patients that cataract surgery isn't as accurate as LASIK, and I tell them why. When they finish our [practice's] education, they understand the variables of effective lens position and incisional healing and how they can negatively affect the accuracy of the result. I go on to explain how with every other implant it's not unusual for me to say that 'I wish I had known your healing was going to lead to the blur without glasses you're experiencing because then I would have put in a different power implant. With the LAL that's less of an issue because when the healing has stabilized, we simply change the power of the implant to the power meant for you and that's why it's [incredibly accurate].'

"When we start talking about the LAL's LASIK-like accuracy, patients almost hear the word 'perfect,' " continues Dr. Thompson. "That's why it's so important to set up expectations. Some patients may still need to wear glasses for viewing certain things."

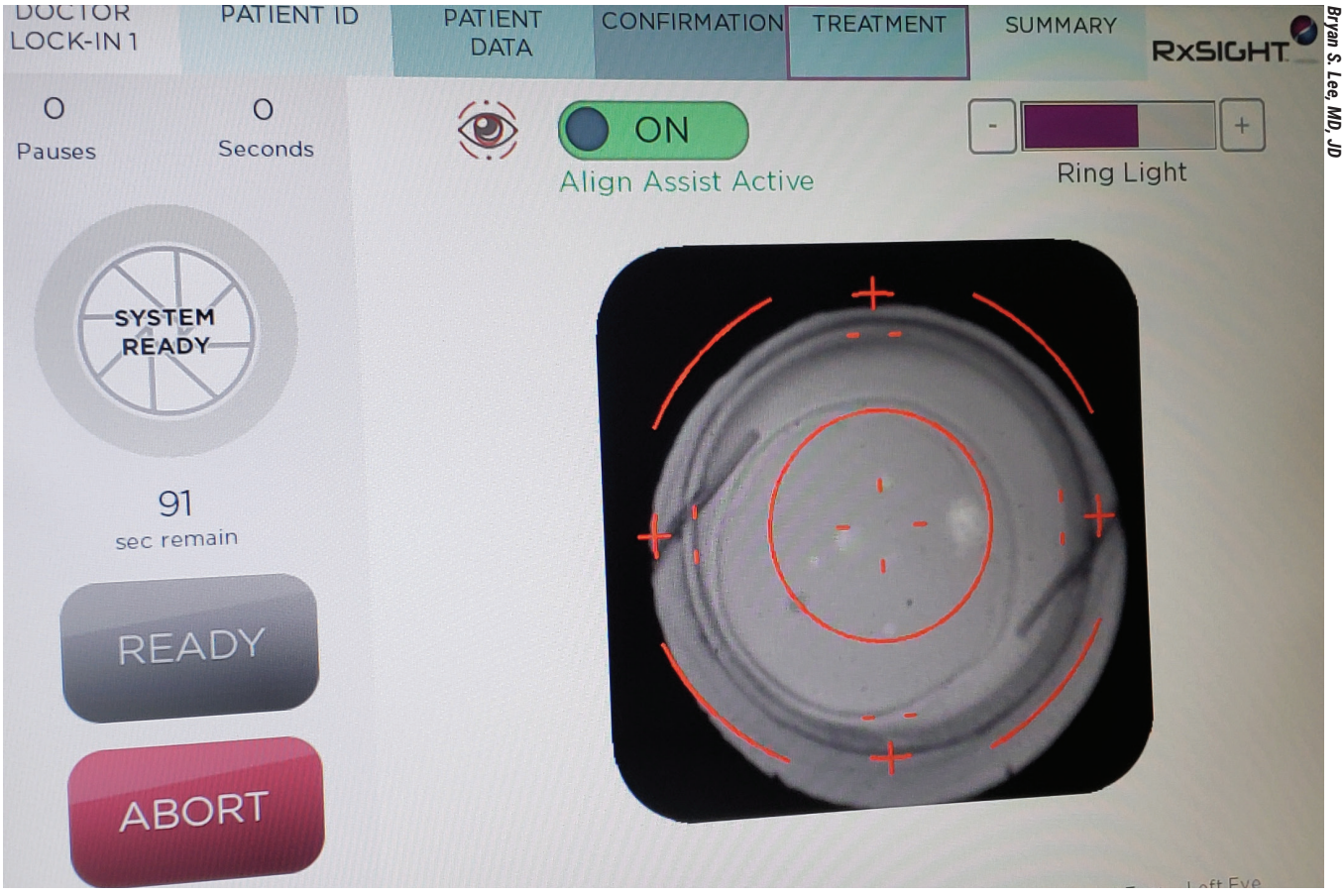
"The art of sales isn't something that's taught in medical school or during residency, and it's not a natural transition for most surgeons," Dr. Vukich says. "It's very hard to take that step. However, I've learned that the way I present things is ultimately how I'm providing information, and the patient needs to make a decision. Don't oversell the technology but be honest about the strong outcomes. At the end of the day, a premium lens is a product you sell. What I'm selling isn't something that doesn't have value. I'm providing the opportunity for a technology the patient might not have known even existed."

Navigating the Postops

The first months after receiving the LAL involve more visits than the average cataract experience, Dr. Thompson explains. "In addition to the healing visits at one day and one week, there are the light adjustments and lock-in visits," he says. "As with traditional cataract surgery where there's a period of waiting for the patient's refractive error to stabilize before prescribing glasses, LAL patients must wait four or five weeks to stabilize before undergoing light treatments."

"There's no question that the LAL adds chair time," agrees Dr. Vukich. "Adjustment visits aren't simple 'how are you doing' visits with the patient on their way in five minutes. These patients have to be refracted and dilated and then treated."

"Some patients are slow dilators," Dr. Lee adds. "Also, they have to dilate beyond what we need to see



Bryan S. Lee, MD, JD

The Light Delivery Device screen just before initiation of a treatment. Patients typically undergo three light adjustments and two lock-ins, but some patients require fewer treatments.

the retina and lens during a typical eye exam. For light adjustments, we really need patients to dilate all the way to the edge of the lens. Some patients dilate with one or two sets of dilating drops, and others take four or five sets. They take up a room and are there for quite a while. We learned not to start LAL patients too late in the day."

"Typically, we do three light adjustments and two lock-ins, though sometimes the patient doesn't need all five treatments," Dr. Thompson says. "The Light Delivery Device performs a mathematical equation that ensures all the macromer (the unpolymerized polymer) in the lens is fully polymerized. That may take five treatments or fewer."

Dr. Thompson says hand positioning for the light delivery is very intuitive. "It's similar to if you were doing gonioscopy or YAG laser capsulotomy," he says. "The learning curve is short because of that."

At his practice, Dr. Thompson says it's pretty unusual to perform more than two treatments in one week. "You should be able to do a treatment every two or three days, in theory, but we typically don't push it to that limit," he says. "We often do two treatments in one week, and the following week do another treatment and begin the lock-in process. If necessary, we do the final lock-in during the third week."

Workflow Changes

Dr. Marvasti's practice was among the first to offer the LAL. "We learned as we went, but I wish we'd had someone to give us advice," he says. "Now you're going from a patient who—apart from the day of surgery—you saw maybe three or four times for postop visits to a case where you're going from preop and surgery to five, six—sometimes seven or more visits. Your office is going to get busier; your waiting room is going to get busier. Your wait time may increase if you don't make changes at each stage. It's almost like adding 10 to 20 percent volume to your clinic and to your optometrist's clinic, so you have to prepare for that."

Dr. Lee's practice began offering the LAL soon after its approval, which also coincided with the COVID-19 pandemic. Despite pandemic disruptions, he says the slow-down in patient volume gave his practice the opportunity to try out different workflows for LAL patients. "Now, patients undergoing light adjustments tend to be scheduled first thing in the morning or the first slot of the afternoon,"

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he explains. "Our Light Delivery Device is in the same room where we have a lot of our other testing equipment, which is on the opposite side of the building from where we see patients. It's more efficient for us to have these patients stacked up and ready to adjust, as opposed to being scattered throughout the day. We bring them over to the testing room and do light adjustments for two or three patients at a time.

"My partner does it differently," Dr. Lee continues. "He does light adjustments after his OR days, so he comes back from the OR and has his patients already worked up and dilated. Each practice will have to figure out what works best in terms of integrating LAL patients into workflow."

At Dr. Vukich's practice, an optometrist refracts the patient at each light-adjustment visit and provides the discussion of the refractive outcome. "In some instances, they'll have the machine programmed and I'll come in and do the treatment. If the patient is seated and the treatment is already registered to the machine, chair time may be as little as three minutes, including a bit of chit-chat. This approach is very efficient, but it's vital to have someone with the skillset of a quality refractionist who also understands patient relations. That's the person you need to have in your office to facilitate."

Dr. Thompson emphasizes the need to set up your team's and referring doctors' expectations for the LAL process. "You're doing everything in a six- to eight-week period for these patients," he says. "It's important for the team members to prepare themselves."

Since patients must return to the clinic so frequently within a short period of time, Dr. Thompson recommends working out a way to streamline these light-adjustment visits. "It's not unusual for these to be two-hour visits," he says. "We don't want patients spending a lot of time in the waiting room. We streamline getting them back, getting their uncorrected vision checked, doing their manifest refraction and getting them dilated. We want to have that beginning step before dilation happen quickly because, as we all know, dilation can't be sped up, and we want the pupil to dilate to at least 6.5 to 7 mm. In certain patients, additional dilating drops or even a pledget to hold the dilation drop on the eye longer may be needed. However, the light-adjustment process itself is only about five minutes, if you include double-checking data entry, alignment and the 60- to 90-second light delivery."

Amir Marvasti, MD

Amir Marvasti, MD, of Coastal Vision Medical Group in Orange County, California, performs a light treatment on an LAL patient in his office.

The Right People & Tools

The surgeons we spoke with for this article say the LAL accounts for approximately 15 to 30 percent of their premium lens volume. Experts note that in a high-volume practice, in particular, the additional postops may require some other changes.

"You may need to add additional optometrists to your practice, depending on your LAL volume," Dr. Marvasti notes. "Good refractionists are absolutely necessary. You'll also have to decide how many Light Delivery Devices to acquire. If you're a single-location practice, just one

of the Light Delivery Devices is sufficient. But if you have multiple locations, at some point you have to make a decision: Do you just want one of these and have your patients travel or would you like one device per location?"

It's also key to have a way of tracking patients' light treatments. Dr. Marvasti's practice uses a paper chart to track every patient's progress as well as LAL-specific notes in their EMR system. "You need to keep track of many aspects, and this amount of information may not fit in a regular EMR visit or just be difficult to track," he says. "What was the preop refraction? The one-week refraction? The two-week refraction? Was a contact lens trial for monovision done? If so, what was the result? What were the results for the first, second and third treatments?"

"For us, it's pretty straightforward since we're on paper," Dr. Lee says. "What's nice about the paper chart system is that it's just two or three pages. We can easily flip back and see the entire time course. Apart from the numbers, it's also a quick reminder of what the discussion was with the patient, why we planned the treatment a certain way and what the patient's feedback was each time. I think it'd be much more cumbersome to do that with EMR."

How Much to Charge?

How practices choose to price the LAL varies. Some practices charge more due to the additional amount of time and labor while others have opted to charge the same amount as they would for a trifocal or EDOF lens.

"We charge the same as we do for a trifocal or EDOF because it's about the same number of visits in a year, just more condensed on the front end," Dr. Thompson says. "The LAL has been a game-changer in our practice."

At Dr. Vukich's practice, he says they charge almost the same as what they charge for a multifocal lens. "Many practices charge more for the LAL because there's more work involved," he points out. "I want there to be a premium lens that's the best choice for the patient—not a good-better-best option—and not a price-related decision."

Dr. Lee's practice charges more for the LAL than a trifocal because "it involves so much postop care and time."

Dr. Marvasti says his practice initially priced the LAL as a presbyopia-managing lens with laser-assisted cataract surgery. Over the years, they increased the price by 10 to 15 percent to account for the additional visits and work involved with the lens. "The LAL price is an easy discussion with the patient compared to other presbyopia-managing lenses," he explains. "With a trifocal, for instance, you're telling the patient that the cost is related to their ability to read. With the LAL, it's very easy for patients to understand why it would cost more given the amount of work that goes into each of the many visits. The real question is: 'This is a monofocal. Why should I go through with this cost?' That's a whole discussion on the differences between an adjustable monofocal IOL and non-adjustable IOLs for a particular patient."

Commitment

"The LAL is a great technology, but to be successful with it, you have to fully commit to making the necessary logistical adjustments," Dr. Lee says. "Offering the LAL isn't something you can do in a part-time fashion. It wouldn't lend itself well to a roll-in roll-out model where you don't own the device, but it comes to your practice on certain days. I think it'd be very hard to do that."

He adds that it's a full team effort. "Your scheduler, your front desk staff, your technicians, and your optometrists have to understand that there will be some major changes in patient flow and other areas. Everyone needs to understand why you're adding the LAL, why the technology is so different and why it works the way it does."

> **If you already do LASIK, you can use that as a model and apply it to cataract surgery [with the LAL].**
>
> ***— Amir Marvasti, MD***

Dr. Marvasti advises prospective LAL surgeons who don't already perform LASIK to consult with colleagues who have busy LASIK days. "See how they manage all their refractions or how many optometrists they have," he says. "If you already do LASIK, you can use that as a model and apply it to cataract surgery. Overall, consulting with physicians who have been using the LAL or their office managers will help because you'll have to change your templates and potentially add more staff. Whether or not you're willing or able to do that is very important."

What about surgeons who want to offer the LAL but feel their practice is already too busy? "Busy is not the same as productive," Dr. Vukich says. "Realigning your priorities and how you allocate your time can be to your advantage economically and to the advantage of the patients you treat. Don't just say, 'Oh, I see too many patients the way it is now.' Are those all the patients you want to be seeing? Are these patients who could maybe be seen by an optometrist instead for routine visits and follow-ups? Are

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Indication

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Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

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*Xiidra reduced symptoms of eye dryness at 2 weeks (based on Eye Dryness Score compared to vehicle) in 2 out of 4 studies, with improvements observed at 6 and 12 weeks in all 4 studies.[1†]

Important Safety Information (cont)

- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Important Product Information on adjacent page.

†Pivotal trial data

The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0-4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0-100).[1]

Effects on symptoms of dry eye disease: A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials.[1]

Effects on signs of dry eye disease: At day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 of the 4 studies.[1]

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **2.** Data on file. DRF Fingertip Formulary® Novartis Pharmaceuticals Corp; July 2022.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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you spending your time efficiently and productively? It's not a numbers game in terms of the number of patients in your waiting area. It's about quality versus quantity. A doctor who does 10 premium lenses compared with one who does 30 standard implants with no premium conversion wins every time."

As a disruptive technology, the LAL's initial incorporation into a practice can be challenging, but surgeons say the outcomes and the patient and staff enthusiasm are well worth the changes. "It's been refreshing having so many happy patients," Dr. Vukich says. "It's easy to see everyone's enthusiasm. Patients in the dilating area are talking about how great their vision is, and it boosts the morale of those about to get their first light adjustment and creates a general positive feeling throughout the clinic for the staff as well. It's been a practice builder too. At the end of the day, if you're delivering outstanding results, word gets out, and word of mouth is a major driver."

Vance Thompson, MD

Adjustments are performed using the Light Delivery Device. Experts note that since some patients may take a while to dilate, it's best to avoid starting LAL patients too late in the day.

Adjustable Technology In the Pipeline

The LAL is currently the only available adjustable lens technology, but experts are looking forward to a few others in development. Here are some in the pipeline:

• ***Perfect Lens.*** Perfect Lens technology uses low-level femtosecond laser energy to alter the hydrophilicity of a hydrophobic acrylic IOL's polymer. It's done in a pattern called "phase wrapping" that slowly builds a change in an IOL's subsurface, effecting a change in the lens itself, explains Nick Mamalis, MD, of the Moran Eye Center at the University of Utah and member of the Perfect Lens advisory board. "It can make not only spherical but also toric corrections on the lens, so one could potentially place a multifocal pattern on the lens, if that's something to be desired," he says.

"This technology can also correct the power of a lens that's been in the patient's eye for quite some time," he continues. "It could be done right after the initial surgery once the patient's refractive changes settle down and they've got significant refractive error. But it could also change a lens that's been in a patient's eye for years, as long as the pupil dilates enough to provide a clear view of the lens itself."

The setup is similar to that of femto cataract surgery, Dr. Mamalis says. "A special coupling lens is placed on the eye and then the laser will come in and focus. Once the focusing is done and the patient is set up and ready for surgery, the procedure itself takes just a couple of minutes. The laser treatment is usually done as a one-time procedure, but it could be done more than once, if a patient's refraction changed years later."

The Perfect Lens group has been conducting extensive laboratory research and reports that changes can be made within 0.1 D. "It's very precise," Dr. Mamalis says. "There have been multiple studies done on research eyes showing very accurate lens changes. The company was just beginning to do clinical studies outside of the United States when COVID hit, so there was a two-year delay in living human eyes, but they're now in the process of conducting studies that will allow Perfect Lens to get a CE mark in Europe and eventually get FDA approved in the United States."

• ***LIRIC.*** Laser-induced refractive index change (LIRIC) is in early stages. It could potentially induce power changes in an IOL, though now it's currently being investigated for use on the cornea.

The technology, piloted by scientists at the University of Rochester and licensed to Clerio Vision, uses low-level pulsed femto laser energy to non-surgically alter the refractive index of certain materials and tissues such as the cornea, crystalline lens, intraocular lenses and contact lenses. According to the University of Rochester, this process doesn't induce a healing or scarring response and can be customized to an individual's exact wavefront error in the eye.[1]

You can read more about LIRIC in the February 2022 issue of *Review* and in the feature, "Refractive Procedures in the Pipeline" on page 50 of this month's issue. ◀

1. LIRIC – a new paradigm in refractive error correction. University of Rochester Medicine, Flaum Eye Institute. https://www.urmc.rochester.edu/eye-institute/research/labs/huxlin/projects/liric.aspx. Accessed March 9, 2023.

SURGICAL PEARLS FOR GONIOTOMY

Glaucoma experts offer pearls and guidance for this popular MIGS procedure.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Goniotomy is a popular MIGS choice for many surgeons since it can be done as a standalone procedure or in conjunction with cataract surgery, has a low upfront and per-case cost (if using a manual blade such as the Kahook Dual Blade), and provides a safe and effective way to lower intraocular pressures without blebs or implanted devices. Jonathan S. Myers, MD, a professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University and chief of the Wills Eye Hospital Glaucoma Service in Philadelphia, notes that "for many clinicians who aren't glaucoma specialists or who don't predominantly see glaucoma patients, it can be easier to have one go-to procedure rather than six different procedures that they're not going to do often."

Here, surgeons share their pearls for performing a successful goniotomy.

Choosing Good Candidates

Patient selection for goniotomy involves many factors, explains Dr. Myers. "Patients fall into a couple groups," he says. "Some patients might have relatively mild or moderate glaucoma but a diagnosis that precludes the use of a device such as an iStent or Hydrus. A goniotomy may make sense for them if they're close to their pressure goal and the primary reason I'm doing goniotomy is to reduce their medication burden or lower their pressure just a few points.

"Patients who have secondary glaucomas and are generally younger may be good candidates for goniotomy as an alternative to filtering surgery when they need a substantial pressure reduction," he continues. "For these patients, there's a better chance that goniotomy can give them this substantial pressure reduction compared with routine geriatric POAG cases that need pressures reduced from, say, 30 to 15 mmHg. Those results are often disappointing."

He says that patients who have a high risk for postoperative bleeding in the first week or later on in life may be poor candidates for goniotomy. "Those patients may do a lot of Valsalva-type maneuvers for weightlifting or have issues that trigger Valsalva such as chronic cough or obesity," he says. "Goniotomy also isn't my first choice for patients taking strong blood thinners or those who have only one eye. There's a fair chance of hyphema in the first week after goniotomy which can substantially reduce vision. For monocular patients, goniotomy isn't high on my list either. For any of these patients who may be at greater risk for certain difficulties in the postop period or later, education is important, so they understand the pros and cons of goniotomy and whether it's the right choice for them."

Does the size of the goniotomy matter? "I think a 90-degree goniotomy probably has less risk than a 180-degree or a 360-degree goniotomy, but we don't have studies to prove that," Dr. Myers says. "I'd do a 90-degree goniotomy during cataract surgery in a patient who's just trying to get off a couple of eye

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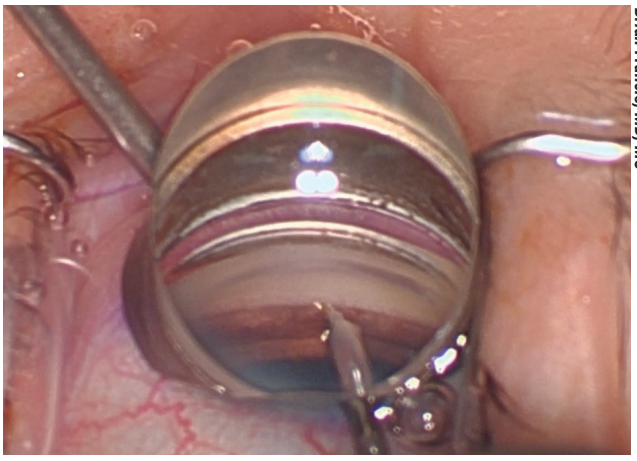
Dr. Ragusa has been a speaker for New World Medical in the past. **Dr. Myers** is a consultant for AbbVie, Aerie, Avisi, Embark Neuro, Glaukos, Haag Streit, MicroOptx, Olleyes and conducts research for AbbVie, Aerie, Equinox, Glaukos, Guardian, Haag Streit, Laboratories Thea, Nicox, Olleyes and Santen. **Dr. Francis** is a consultant for MST and New World Medical.

drops; or in a patient who needs a slight pressure reduction with modest IOP goals. I try to err on the side of caution and not subject the patient to a greater risk of hyphema in the first week since the goniotomy is for a relatively less critical indication."

To reduce the risk of hyphema, experts say restricting certain activities and leaving the pressure high at the end of the case can help. "I'd rather have the patient's pressure at 25 or higher right there in the operating room than have it low," Dr. Myers says. "A transiently high pressure can prevent a bleed that might lead to a significant IOP spike later."



Brian Francis, MD, MS

Figure 1. Surgical view of the approach to trabecular meshwork with a goniotomy dual blade device. Angling the tip of the device at an upward angle helps it to pierce the trabecular meshwork for the initial entry into Schlemm's Canal.

Gonio Lenses

Choosing a gonio lens comes down to surgeon preference. Some have handles, some consist of a floating eyepiece on a ring with small protrusions (resembling a Thornton ring) for stability and others have no handle and float on the eye itself with the coupling agent. Dr. Myers says he usually uses a gonio lens with a handle.

"For the combined gonio lens on the Thornton ring, the stability ring allows the surgeon to fixate the eye very precisely and rely less on the patient maintaining gaze in the right direction," he says. "This can make a tough procedure much easier because you have this additional control. It's always frustrating when you have a perfect view, and you go to do the goniotomy or other angle procedure and the patient starts moving or moving their eye around."

The free-floating eyepiece allows the surgeon to have their hands free. "This can be a real advantage especially if you're early in the learning curve," Dr. Myers notes. "There's nothing wrong with using your nondominant hand to support and add precision to your dominant hand as it's learning the motions of goniotomy or other angle procedures. These lenses also provide a slightly wider view."

Goniotomy with Phaco

In combined cataract surgery, goniotomy can be performed either before or after phacoemulsification, depending on surgeon preference. "When doing goniotomy in conjunction with cataract surgery, I typically save the goniotomy for after IOL implantation," says Nikola Ragusa, MD, FACS, of New York Ophthalmology in the Bronx. "Removing the cataract helps to open up the angle, and you can almost always see some refluxing blood into Schlemm's canal which can help you identify the trabecular meshwork and see where to aim your tool in trickier cases."

Dr. Myers says he typically performs goniotomy with the KDB before phaco. "The thicker viscoelastic in the anterior chamber at the start of a case often makes for a better view than later in the case, so that's one advantage of doing goniotomy earlier," he says. "Another advantage of doing it in the beginning of the case is that if there's significant bleeding at the start, the pressurization of the eye during phaco with the I/A will usually stop the bleeding before I'm done the procedure. The drawback, of course, is that substantial bleeding early on can make the next stages of the procedure more challenging when visualization can be an issue. In my experience, that's uncommon and very infrequent."

Instruments of Choice

For unroofing Schlemm's canal, surgeons may use instruments such as the Trabectome, Kahook Dual Blade, TrabEx and TrabEx+, says Brian Francis, MD, MS, a professor of ophthalmology at the Doheny and Stein Eye Institutes, Geffen School of Medicine, University of California Los Angeles (UCLA). "The KDB, TrabEx and TrabEx+ are all manual devices that lift and cut two sides of the trabecular meshwork and unroof Schlemm's canal. In contrast, the Trabectome uses an electrocautery unit and a plasma energy wave that vaporizes the tissue. The TrabEx+ and Trabectome use continuous irrigation/aspiration instead of viscoelastic like the KDB and TrabEx."

Dr. Francis says he finds that the electrocautery approach makes tissue removal easy. "With manual goniotomy, you have to be a little more conscious keeping the blade parallel to the trabecular meshwork and of not slicing through tissue," he notes. "If you're at an angle and one blade is cutting tissue and the other isn't really engaging tissue, you might slice through rather than lift and remove tissue.

"As for irrigation/aspiration versus viscoelastic approaches, each has advantages," he continues. "With irrigation/aspiration, you have constant maintenance of the anterior chamber and removal of any refluxed blood. The disadvantage is that the instrument has to fit through a certain size incision. Because you want a good seal of the instrument within the eye and no fluid leakage around

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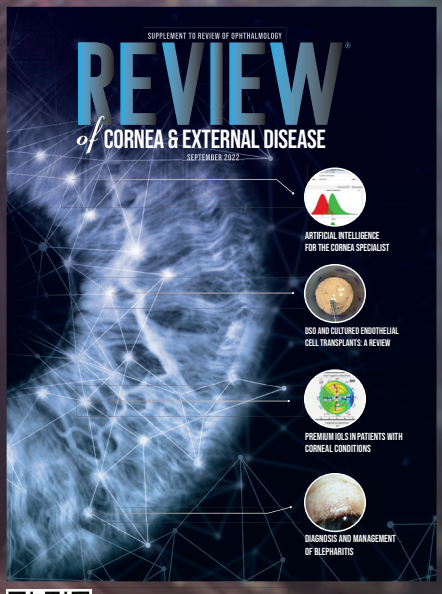

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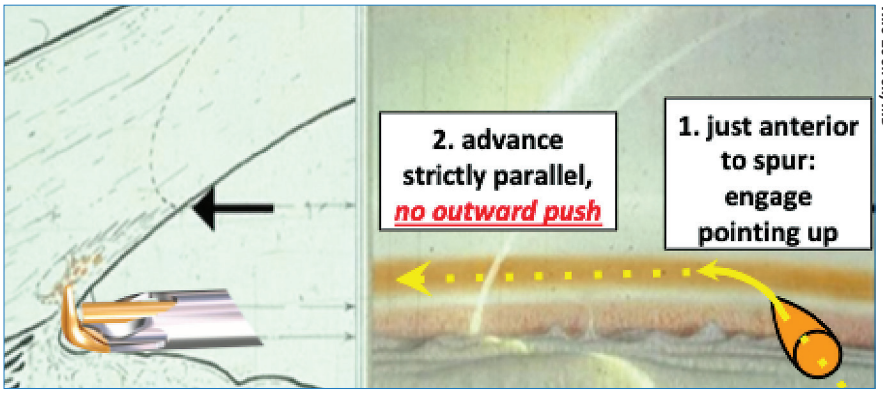
the entry site, you have to match the size of the incision to the width of the instrument. Currently, that's 1.8 mm, so you need a 1.8- or 2-mm keratome. If you do phaco through a standard 2.4-mm keratome incision, it's going to be a bit big for the procedure. Usually in those cases, you'd do the 1.8 keratome first, do the procedure and then enlarge the incision and do phaco afterwards. So, the advantage of doing goniotomy under viscoelastic is that you can do it with any size incision, and therefore either before or after the cataract extraction."

Dr. Ragusa says he uses a Kahook Dual Blade or Streamline for most goniotomies. "I like that the Kahook Dual Blade is designed to fit Schlemm's canal and excise and unroof the trabecular meshwork in a way that causes minimal harm to surrounding tissues and posterior structures," he says. "I've also used the Streamline, which can be billed as either canaloplasty or goniotomy. It's not like traditional goniotomy but it does punch a hole in the trabecular meshwork and allow an egress of viscoelastic material into the canal. It's very gentle and the footplate allows for good positioning. Patients experience a decent IOP drop of around 20 to 30 percent.

"Some patients may have issues with insurance coverage and are stuck between a rock and a hard place with prior authorizations," Dr. Ragusa points out. "The surgery center may not pay for a certain tool, but there are creative things you can do like use a 27-gauge needle with a slightly bent tip. I've done it a few times. It's not ideal, but it's better than leaving it alone."

Anesthesia

Retrobulbar blocks, sub-Tenon's blocks and topical anesthesia may be used. "Topical anesthesia along with gentle sedation will enable the patient to cooperate and position their eye," Dr. Myers says. "I personally enjoy having the patient be able to turn their eye inward toward their nose to gain the best view. If you're using blocks, a gonio prism with an incorporated Thornton ring will allow you to fixate and then move the globe as needed with the guiding hand."



Nils Loewen, MD

Figure 2. Representative drawing of the approach to trabecular meshwork with a goniotomy dual blade device. Angling the tip of the device at an upward angle (1) helps it to pierce the trabecular meshwork for the initial entry into Schlemm's Canal. Once the tip is in the canal, the tip is then turned parallel to the iris and advanced (2).

The Procedure

Once the instrument is in the eye, it's important to avoid getting too close to the cornea or accidentally contacting the iris, Dr. Myers explains. "If you have this in mind, it won't be a problem. Inadvertent damage to nearby structures usually happens if you're not thinking about it," he says. He usually starts in the middle nasally, makes a slight incision, and then sweeps from the inferior angle toward the nasal angle and then from the superior angle toward the nasal angle for a limited goniotomy with a KDB or cystotome. "This usually leaves a free strip that's easily removed. If you leave the strip, I don't think that's the end of the world, but it looks less neat."

Dr. Ragusa also uses the inside-out technique, starting in the middle and sweeping in either direction. "I do my cases with topical anesthesia," he says. "With less security against the patient moving, this technique allows me to do the goniotomy a little quicker."

"If I'm doing OMNI 360," Dr. Myers adds, "I do viscodilation first, injecting inferiorly and then superiorly, and then tearing 180 degrees inferiorly or doing both the interior and superior on the second pass."

Dr. Francis' preferred technique uses the Trabectome and the inside-out approach. "I go forehand and backhand," he says. "I'll advance straight across to the nasal meshwork, right across from my incision, and engage the tissue. I go forehand, which for a right-handed surgeon is a counterclockwise movement, and then I'll flip the instrument 180 degrees and engage it back where my incision started and go back in clockwise. I find this approach easier in terms of engaging the trabecular meshwork. If you're left-handed, you'd do the opposite—clockwise and then counterclockwise."

He says that engaging the tissue directly across from the incision is often easiest. "Some surgeons will go in one direction, starting as far over as they can and sweeping all the way in one direction counterclockwise. There's nothing wrong with that, but it can be harder to engage the tissue when the instrument is at an angle. Assuming an en face approach, where the trabecular meshwork is facing perpendicular to the blade, will help."

At the end of the case, experts say to aim for higher pressures and gently titrate the pressure down to avoid hyphema that could occur overnight

or a few hours postop.

Pearls for Success

Here are some pearls for ensuring a smooth goniotomy:

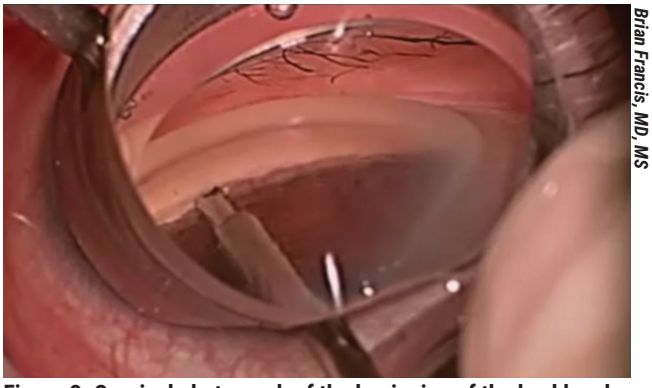
• ***Consider patient mobility preoperatively.*** When considering a patient for any angle-based surgery in the office, Dr. Myers says to take a good look at the patient. "If the patient is kyphotic and hunched over, they may not be able to lie flat," he notes. "Some patients can't turn their heads to the side or extend their neck. If they have a large arcus senilus, that will make it harder to see the angle. All of these things can make a simple procedure extraordinarily difficult, so be aware of these possibilities and take a second to think when you sign up the case. It can save you a lot of gymnastics in the OR."

"Patients need to be able to tilt their head at least 30 degrees," Dr. Ragusa says. "If they're not able to, you can do a really severe tilt in the scope to help with visualization."

• ***Iris processes may indicate unsuitable patients.*** Patients with extensive iris processes may be poor goniotomy candidates, Dr. Myers explains, because "it's easy to put traction on the iris root, causing bleeding and other problems. I'd think of doing a different procedure in a patient whose angle anatomy is either hard to fully understand or has issues that may obstruct the easy passage of your instrument. Similarly, if you're dissecting PAS, do this with great care. If there's bleeding from synechial dissection, the whole procedure becomes harder."

"Most of the time, you can gently sweep away the PAS with either the goniotomy device or with a little bit of extra I/A to help peel it away," Dr. Ragusa adds.

• ***Be prepared for the lightly pigmented patients.*** Experts say that performing gonioscopy preoperatively will ensure there's no surprises when you perform the goniotomy. Also for patients with lighter pigment, Dr. Ragusa says a bit of blood reflux into Schlemm's canal will help you see where you're going. "Lowering the pressure and not having too much viscoelastic in the eye can help because the blood will paint it," he says. "Some surgeons use trypan blue to stain the angle."



Brian Francis, MD, MS

Figure 3. Surgical photograph of the beginning of the backhand pass of a surgical *ab interno* goniotomy. (The instrument shown is the Trabectome.)

• ***What sometimes looks like great surgeon skill is partly great skill in setting things up.*** The goniotomy setup process can pave the way for an easier surgery. "Positioning the scope and the patient's head is key for visualization," Dr. Myers says, noting that the patient's head should be tilted about 30 to 40 degrees away from you. "A clear view of the anatomy makes a difference in the difficulty level of goniotomy."

• ***Ergonomic injuries are common among ophthalmologists.*** Be mindful of your body position. Goniotomy is about visualization and small precise movements, Dr. Myers says. "If your hands aren't in a comfortable position, it's hard to be as precise in your movements within the eye," he says. "I usually have my ring finger and pinky finger against the patient's forehead and cheek."

Wrist rests, commonly used by retina specialists, are one tool that can help stabilize a surgeon's hands. These U-shaped devices go around the patient's head and sit at about ear level. "Wrist rests make it very easy to sit your hand on the bar, and your hands are remarkably stable," Dr. Myers says. "If you're not using a wrist rest (like most anterior segment surgeons) having your fingers against the patient's face is very helpful. Be sure do to it in such a way so you're comfortable based on the bed position and scope position. You shouldn't be hunching your shoulders to get your elbows and arms to the right height or extending your neck. Extending your neck to the scope is one of the most common ways to get an ergonomic injury in ophthalmology."

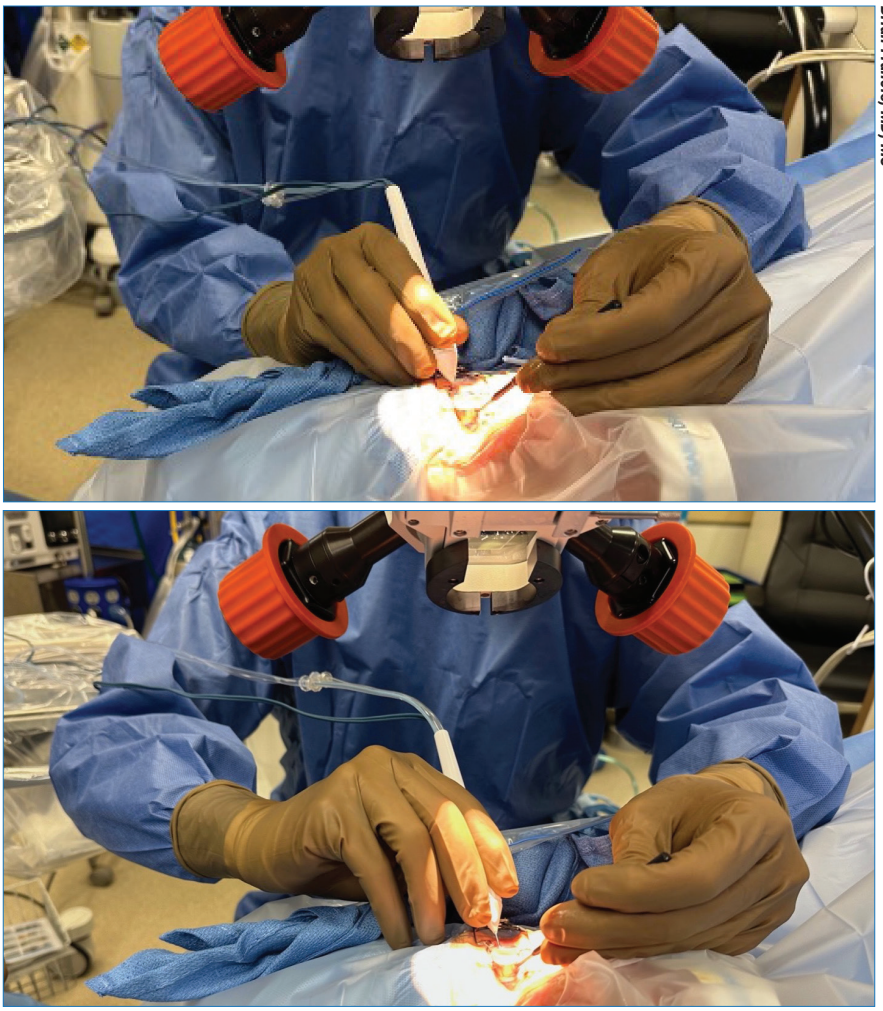
• ***Take your time to establish a good view.*** "Be sure to take your time until you establish a good view because even if there's a little bit of blood, it'll get worse once you start manipulating the eye," Dr. Ragusa says. "Try to clean blood away from your sights and your gonio lens."

• ***Don't put too much pressure on the back of the wound.*** "Surgeons who are less familiar with angle procedures often place too much pressure on the back of the wound with the dominant hand, causing egress of viscoelastic and distorting the view through the cornea," says Dr. Myers.

• ***Pivot at the wound, not within the eye.*** Pivoting at the wound is critical, Dr. Myers explains, "because as you get to the edge of the wound, if you're putting pressure on it, you tend to degrade the view and the pressure there makes your movements less precise within the eye.

"In order to swing correctly in the nasal angle where you're doing the goniotomy, you need to have the right pivot point and arc, starting at that pivot point at the temporal incision," he continues. "You want to match your arc with the curvature of the eye for precise removal of tissue and to avoid getting into trouble by either going too anterior toward the cornea or too posterior toward the ciliary body."

• ***Don't grab the back wall.*** This makes for a less smooth and predict-



Brian Francis, MD, MS

Figure 4. Photographs of hand and arm position during surgical goniotomy. The top photo shows the standard grip for the forehand pass, which is from left to right in this view (counterclockwise for the surgeon). The bottom photo shows the hand and arm position for the backhand pass, in which the instrument passes from right to left in this view (clockwise for the surgeon). Note the elbow is slightly raised and the forearm and hand are turned to allow for flexion of the wrist to advance the instrument (rather than extension), which is a more natural and controlled motion.

able goniotomy. There should be almost no resistance when performing goniotomy. Experts say that if you feel resistance against your blade, the instrument is either wedged against the incision or you've gone too deep and are engaging the sclera in the back of Schlemm's canal. For those not used to angle surgery or making the arc, it can be easy to engage the back of Schlemm's canal.

"Once you go one or two clock hours, you'll notice that you have to readjust the tip because the arc of your approach doesn't exactly match that of Schlemm's canal—it's shallower," Dr. Francis says. "The tip of your instrument will start to embed itself into the sclera, so you have to pull back a bit and turn the instrument to adjust the arc of approach to stay within Schlemm's canal and avoid digging into the sclera. If you see some eye movement or the instrument isn't moving as smoothly, that means you're in too deep and need to back off.

"Another thing you can do is angle the tip of the blade a little upwards as you enter the trabecular meshwork," he says (*Figures 1 and 2*). "For your first entrance, instead of going parallel to the trabecular meshwork and iris insertion, come upward at a little bit of an angle. That allows the tip of the instrument to pierce the trabecular meshwork. Once that's done, you go parallel to the trabecular meshwork and Schlemm's canal and proceed smoothly along in the canal" (see *Figure 2*).

"When everything is lined up well and you've done many goniotomies, it's often a relaxed and straightforward procedure that doesn't take much time at all, regardless of which technique you use," Dr. Myers says. "However, early in the learning curve as you gain precision and learn to find the best views and comfort, things are often more challenging."

• ***Change hand positions for the backhand pass.*** Dr. Francis says the backhand pass (*Figure 3*) can be tricky but made easier using certain hand positions. "As a right-handed surgeon, after I flip the instrument over 180 degrees so it's pointing in the opposite direction, I hold the instrument with my left hand and rotate my right hand on the instrument counterclockwise. As I do this, my elbow will come up from a four or five o'clock position to a three o'clock position (*Figure 4*). This rotates your wrist so you can make use of the wrist's natural flexion toward the palm instead of backwards. I find it's easier to perform the motion for the backhand pass this way."

• ***Leaving a little undone is preferable to an imperfect goniotomy.*** For surgeons who don't perform goniotomy often or who are early in the learning curve, Dr. Myers advises, "If you're at a point when you're trying to get that last bit to make the widest goniotomy and either the view isn't perfect or your hand position and comfort aren't perfect, leave it be. If the patient moves or if your movements aren't precise because the view isn't right, a cyclodialysis cleft or other intraoperative complication isn't worth getting that extra clock hour of goniotomy."

THE PRINCIPLES OF REFRACTIVE SCREENING

From advanced diagnostics to patient expectations, refractive surgeons have a wealth of information to consider before counseling patients on LASIK, PRK or SMILE.

LIZ HUNTER
SENIOR EDITOR

The demand for corneal refractive surgery has been growing year by year, and laser vision correction volume topped out at 833,000 cases in 2021, according to the American Refractive Surgery Council. Whether patients come see refractive surgeons out of their own curiosity or because they know a friend or family member who had a procedure, the screening process must be thorough. Technologies and techniques have improved greatly, but the threat of post-surgery ectasia is always in surgeons' minds, and the more preop data they have about patients the better. We spoke with some experienced refractive surgeons about their screening protocols and what influences their decisions to perform LASIK, PRK or SMILE.

Patient History And Expectations

Although technology is a major aspect of the screening process, surgeons must also take cues from conversations with the patient to guide their decision. Not surprisingly, many patients come in requesting and expecting LASIK specifically, unaware of the qualifying factors for it or that there are other options.

"LASIK has become a household name," says Sumitra Khandelwal, MD, associate professor of ophthalmology at Baylor College of Medicine, Cullen Eye Institute. "It's kind of like Kleenex for soft tissues. Even to this day, most patients come in asking for LASIK because they heard I did it on their friend, sibling or parent, but I'll often tell them, 'No, I did PRK,' and they don't even realize what their friend had done. It's really interesting how that stamp gets put on all corneal refractive procedures, even when somebody didn't have LASIK."

It can be eye opening for patients to learn about the alternatives to LASIK and what goals each surgery can achieve. Sometimes surgeons have to deliver a reality check.

"The first conversation I have is about the patient's expectations," says Brad Kligman, MD, whose practice is in Manhasset, New York. "Even before I specifically point to the imaging, I take into consideration the patient's age and what they're coming in expecting to achieve. At least once a month, I have someone in their late 40s/early 50s who are now presbyopic, hates that they have to use their reading glasses, and has the impression that LASIK can fix all of that. I have to explain to them that 'Yes, we could correct your vision to allow you to read, but really the two options for that are to correct both eyes for near and take away your distance vision completely, or correct one eye and create a monovision situation,' which some people are very happy with, but a lot of people, once they hear that we can't restore their eyes to when they were 20 years old with perfect distance and reading vision in both eyes, they say 'Oh, that's not necessarily what I was looking for.'"

John Doane, MD, FACS, of Kansas City, says these patient-centric factors have to be considered. "You have to consider why this person is here. What do they want to get out of the

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Dr. Dell is a consultant to Allergan, Bausch + Lomb, Johnson & Johnson, Lumenis, Optical Express and RxSight. **Dr. Doane** is a consultant to Zeiss. **Dr. Khandelwal** is a consultant for Alcon, Bausch + Lomb, Johnson & Johnson and Zeiss. **Dr. Kligman** receives research support from and is a consultant for Dompe Therapeutics and receives research support from Aerie Pharmaceuticals.

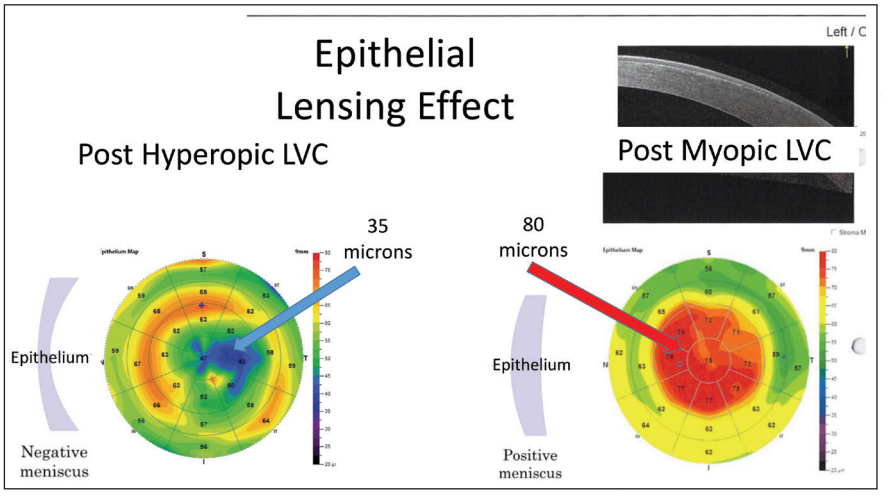
surgery? How old are they? What's their job? You have to understand where people are in their life cycle as far as accommodation, and this sets the tone for what you're going to be counseling them on," says Dr. Doane. "If someone is 50 and they're nearsighted -2 and they want to see great at distance but they don't want to wear glasses when using the computer, well that's not going to work. You have to either change expectations or simply not do surgery."

Patients are often screened in advance by technicians who ask multiple questions about their health and ocular history, but Dr. Khandelwal says she likes to hear the answers for herself. "It's amazing how many times they'll say one thing to the technician and then when I ask them again, they'll change their minds about the answer," she says.

After the usual, "What brings you in today?" question, here are examples of things Dr. Khandelwal will ask, along with her reasoning:

• ***What bothers you about contacts or glasses or both?*** "I like to understand if they're truly contact lens-intolerant or just don't want to wear glasses and contacts," says Dr. Khandelwal. "That mentally leads me to look for signs and symptoms of dry eye and allergies, but also just helps me to be aware of the fact that they may be somebody really sensitive about things around their eyes, or if they're a pretty long-term contact lens wearer I know that they're usually a pretty cooperative patient when it comes to doing things around the eye. When they tell me something like 'I hate it when things are around my eye,' we're going to be careful about how we approach their eye."

• ***Has your prescription changed or not?*** "That's actually the question where a lot of times my technician will ask it, and then my technician will check their wear (current prescription that they walk in with) and then when I talk to the patient, they'll say, 'You know what, actually, my vision prescription has fluctuated a bunch over the last couple of years.' This is a question that sometimes needs to be addressed one more time because they start to think back a little bit," she says. "Also, if they're asked if their glasses have changed but they're a contact lens wearer, they often don't change their glasses for years. And it's hard to know how much your contact lens prescription has been tweaked. I make sure the technician asks about both glasses and contact lens prescriptions."



Steven Dell, MD

Epithelial mapping is not only useful prior to laser vision correction, but also when planning enhancements. Epithelial thickness can be quite variable after LVC, but typically is thickened after myopic LVC and thinned centrally after hyperopic LVC. Removing this epithelium can produce refractive surprises that may take many months to resolve.

• ***Do you have a family member who's had refractive surgery and had issues with their eyes, such as keratoconus?*** "It's an important thing to document because we do know that ectasia has some genetic component to it," Dr. Khandelwal says. "If they have a sibling or a first-degree family member who has keratoconus, I'm going to look at their risk factors just a little differently."

• ***When do you get dry eye?*** "As I go through the typical dry-eye questions, I'll ask if it's only when they wear contacts, or just when they wear their glasses, and the answer guides me," she says.

Dr. Khandelwal will also look for red flags during a clinical exam. "I look for things like blepharitis, scarring of the eyelids, sleeving on the lashes, checking that they don't have something like Staph blepharoconjunctivitis or *Demodex*," she says. "Make sure they don't have a lot of inflammation on the conjunctiva, no capillary reaction from severe allergies. The cornea should be nice and clear. Check that they don't have a bunch of blood vessels from contact lens overuse or tight-fitting contact lenses. I do that because those patients are tough—if you have blood vessels that are within the area where you're going to create a flap, that can cause bleeding and heme, and those can be a challenge to then continue the procedure.

"Make a note if they have any corneal scars," Dr. Khandelwal continues. "Maybe they were a previous ulcer patient, maybe they had trauma to their corneas from something mild, but it left a residual slight scar. You have to be careful with those also with LASIK because when you create the flap with the femtosecond, you can get things like vertical gas breakthrough."

Essential Diagnostic Exams

Innovations in the field of tomography, topography, pachymetry, epithelial mapping and more have contributed to the accuracy of refractive screening.

Steven Dell, MD, medical director

of Dell Laser Consultants in Austin, Texas, started performing laser vision correction when it was first FDA approved and recalls when surgeons didn't have that many tools at their disposal. "Topography was really the only thing we had to screen out whether a patient was or wasn't a candidate, along with pachymetry—and in the earliest days of laser vision correction we were using ultrasound pachymetry," he says. "Now, most of us wouldn't feel comfortable performing laser vision correction unless we had not only a topographical image of the interior surface of the cornea, but also views of the posterior elevation of the cornea with devices such as the Pentacam or Galilei. Those have become much more important. For some period of time we were much more concerned about corneal pachymetry, but I think we've become a little less concerned about overall corneal thickness and much more concerned about whether or not the cornea is topographically normal."

Dr. Kligman, who says he's grateful to have had access to these advanced technologies for the length of his career, says he has always used the Pentacam. "It gives me a complete view of the curvature and thickness profile of the cornea vs. piecing together interior topography with ultrasound pachymetry, which gives you a good idea of the shape of the cornea, but it missed out on some of the more subtle hints of a weaker or ectatic cornea," he says. "That allows us to rule them out with a little bit more competency the patients that might be at higher risk for ectasis beforehand, and even with the Pentacam, we have more advanced analysis with the Belin-Ambrosio ectasia risk score and the ABCD keratoconus staging system."

The Belin ABCD keratoconus staging system considers posterior curvature and thickness measurements based on the thinnest point, as opposed to the apex, which may be a better indicator of keratoconus and related ectatic diseases.[1]

In addition to the Pentacam, Dr. Kligman does an OCT of the macula. "I always want to see up front if there's anything unusual or funny going on in the retina that would impact the outcome of the LASIK so that again we can set expectations and say to the patient, 'You have this going on in the back of your eye which isn't impacted by LASIK and might still cause some limitations based on that,' or 'You're ruled out because of this.' Having the OCT to do a quick scan of the retina even before you get to the dilated exam also helps set expectations or eliminate patients upfront in the earliest stages of the evaluation," he says.

Dr. Doane says corneal topography and anterior-segment OCT are the two most important components he considers. "Does the cornea have normal anatomy and does it have appropriate thickness? Does it have any signs of forme fruste keratoconus (FFKC)? You're looking for anything that would show a sign for potential ectasia or anything topographically that makes you think this person may be a FFKC patient. If they are, they're unsuitable for a lamellar refractive procedure," he says.

"We do Placido topography on the patient, which gives us the mires, which yield quantitative information as well as qualitative information as far as their ocular surface disease goes," says Dr. Khandelwal. "If the mires are distorted in any location, if they're irregular, we can start to think about what might be causing that, such as ocular surface disease or maybe ectasia. You're not going to get the ectasia necessarily screened out from the Placido image, but certainly finding little patches of dryness is helpful. We do tear breakup time on the patients, just to understand what that is."

It's a good idea to double or triple check measurements on patients, too, she continues. "A few things that might cause ocular surface disease can include contact lens warpage, so if a patient over-wears contact lenses or if it was a tight fit to begin with, especially with toric soft lenses, the reality is that it may take longer to get the cornea regular," Dr. Khandelwal says. "This is why we'll often do two measurements at a minimum for patients. We use iDesign for example, and I pick the measurement that makes the most sense, but I need to have two measurements that really match up nicely in order to proceed with the procedure."

Another tool in refractive surgeons' armamentarium is epithelial mapping. Although not widely available, Dr. Dell believes it's within the reach of every refractive surgeon and can be helpful in determining whether patients really are good candidates for laser vision correction. "It can give a better picture of whether or not a patient's topography is abnormal because of a tendency towards keratoconus or FFKC, or whether it's something simply related to dry eye," he says.

"Epithelial mapping in particular is very useful when you're trying to plan enhancements, particularly if you're performing PRK because you may have a patient who has a highly unusual epithelial layer, which may be very unusually thick or very unusually thin," Dr. Dell continues. "When you remove that epithelium, you may have a temporary refractive surprise as the epithelium grows back at normal thickness but then reverts to its previously abnormal thickness over a period of several months. The most typical scenario for this is someone who had LASIK several years ago for, let's say, a -8 and they have a very thick uniform layer of epithelium. And then let's say in this hypothetical situation, they undergo cataract surgery and they wind up a -1 after the cataract surgery and someone decides to perform PRK on that patient, removes their epithelium, treats the -1 and the epithelium grows back at 50 microns instead of 80 microns and the patient is a +1.5 for a year before they eventually fade back down toward maybe +0.5. So that's a pitfall that can

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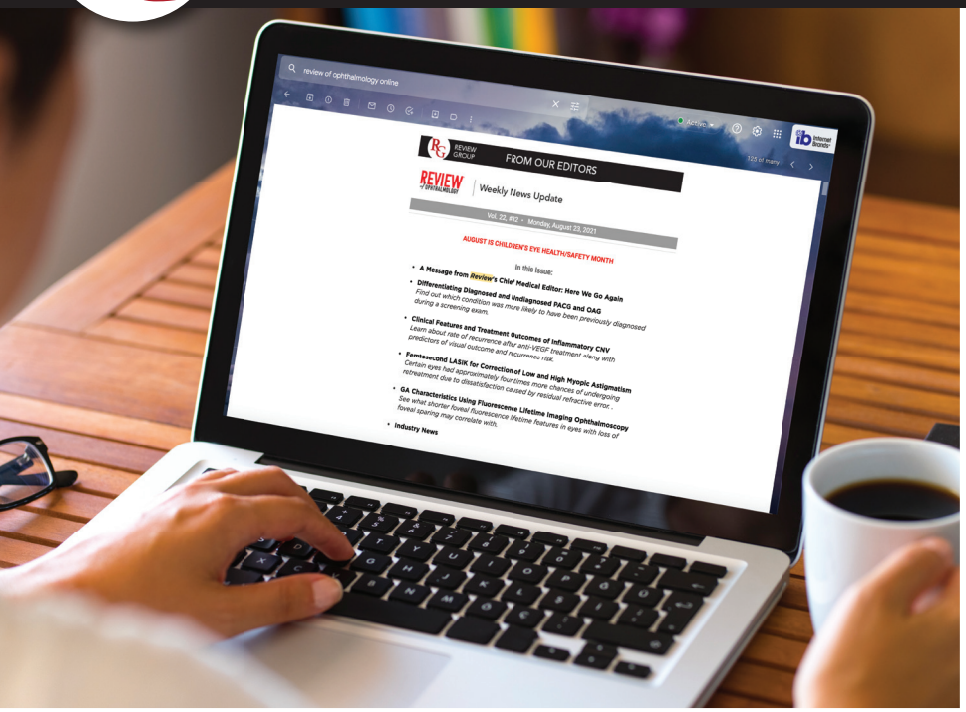

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REVIEW of OPHTHALMOLOGY | Weekly News Update

Vol. 22, #32 • Monday, August 23, 2021

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

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- **Differentiating Diagnosed and Undiagnosed PACG and OAG**
  Find out which condition was more likely to have been previously diagnosed during a screening exam.
- **Clinical Features and Treatment Outcomes of Inflammatory CNV**
  Learn about rate of recurrence after anti-VEGF treatment along with predictors of visual outcome and recurrence risk.
- **Femtosecond LASIK for Correction of Low and High Myopic Astigmatism**
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- **GA Characteristics Using Fluorescence Lifetime Imaging Ophthalmoscopy**
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A message from *Review*'s Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was mildly funny until it wasn't. We had a small happy window of normalcy this spring when marginally successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was

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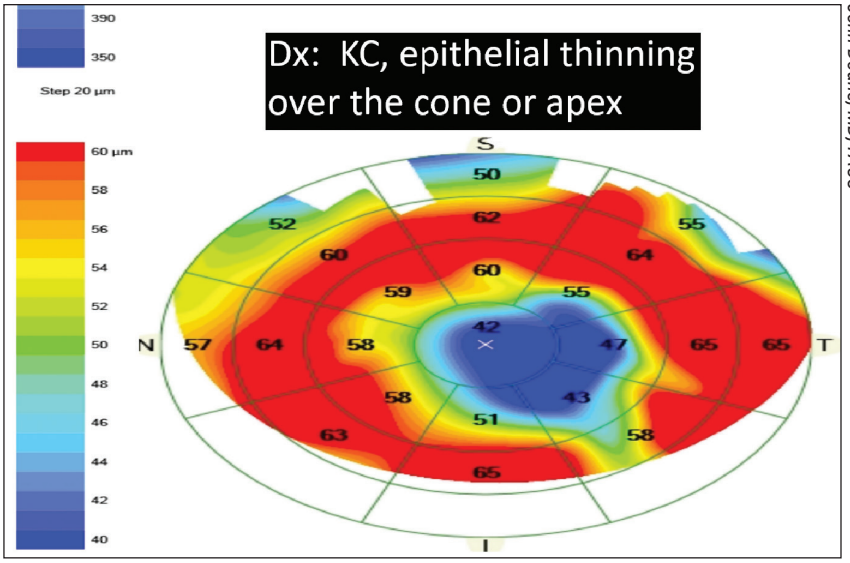
be identified with epithelial mapping before that process even begins."

Dr. Kligman says he'll use epithelial mapping to confirm any suspicions he had about the health of the epithelium. "I've had patients referred to me for keratoconus evaluation who were told they weren't candidates for LASIK and it's happened where the topography and pachymetry didn't match up," he says. "It's important to stain the ocular surface with fluorescein, and for one patient in particular it led me down the path that it could potentially be corneal limbal stem cell deficiency from contact lens overwear, and that's a patient I would take for corneal OCT with epithelial mapping. I could then see that the epithelium was very thickened in that area and it proved the patient didn't have keratoconus, but in fact had an unhealthy ocular surface from abusing their contact lenses." Dr. Kilgman says he treated this patient's corneal surface for about a year and then successfully performed PRK.



This image shows a case of keratoconus with epithelial thinning over the apex, which tells the refractive surgeon that lamellar refractive surgery shouldn't be performed.

John Doane, MD, FACS

Making the Decision

After considering all of the diagnostic and clinical results, refractive surgeons must then determine the best procedure for each individual patient. This can often include delivering disappointing news.

"I think that trying to present the patient with a menu of possible refractive surgery choices and then telling them to pick which one they want is sort of a fool's errand," says Dr. Dell. "The best way to proceed is to identify what you believe is the best procedure for the patient and then tell them that that's what your recommendation is. There are patients who fall into the gray area where they might be a laser vision correction candidate, but they might also be a refractive lens exchange candidate. And in that case, you need to present both options in a coherent fashion with the understanding that this is procedure A and it can correct this list of problems and this is procedure B and it can correct this different list of problems."

Based on the photos, Dr. Khandelwal says she'll already have an idea in her mind of what direction to discuss with a patient. "If they're a really high myope and they have corneas that aren't as thick, I'm going to have a very different discussion with them, as opposed if they're a mild or moderate myope with adequate corneal thickness," she says. "Sometimes I've already decided that they're not going to be a great candidate for LASIK because their visual stromal bed is bad and the cornea that will be left is going to be too thin, in which case I'm maybe having a totally different discussion and perhaps suggesting a phakic intraocular lens such as the EVO, or maybe PRK."

Dr. Kligman is a proponent of visual aids for patients. "I like to look at the images with my patients and explain what we're looking at, and I have models in my exam rooms because there's a lot of confusion among the public about the anatomy of the eye, so I always use a visual aid to point out what the cornea is and what LASIK or PRK is doing," he says. "The color scale is a good way for them to understand astigmatism and if it's a normal bow tie we can absolutely treat that and it's very safe, but if you see these orange or red colors all on one side of the cornea and not on the other side, it could point to a potential risk for a bad outcome."

Most refractive surgeons agree LASIK requires a more perfect topography than PRK.

"Generally speaking, refractive surgeons are more tolerant of slight imperfections in the corneal topography for PRK than we are for LASIK," says Dr. Dell. "A patient's cornea basically has to look very, very normal to perform LASIK, whereas there are some patients who have slight topographic abnormalities that might shift us toward PRK. Other factors that might shift us toward PRK would involve a propensity toward more dryness issues and also the overall corneal thickness and how much tissue will be left behind after the procedure."

Ocular surface issues may steer surgeons away from both LASIK and PRK, says Dr. Khandelwal. "LASIK gets its reputation with dry eye because you're cutting a flap and then you're doing an ablation, but PRK can create dry eye as well because it's an ablative procedure on the cornea and therefore patients can get dry eye with that," she says. "If a patient has a tough ocular surface, they're probably just not a candidate for either LASIK

or PRK and we may talk about an intraocular lens, such as the EVO, or we'll be talking about no surgery because sometimes the correct answer for somebody is actually not to do a procedure and focus on other treatment options, such as changing their contact lens type, getting them out of contact lenses and putting them in a scleral lens, for example. Unfortunately, some patients just aren't candidates for any procedure."

Often, refractive surgeons will want to counsel patients about re-evaluating their options after a few months of treatment. "Eyes that have early or more advanced keratoconus, typically the steeper area would have thinner epithelium overlying that area. If the epithelium in that area is actually thicker, usually it's from contact lens overwear irritation and we can focus the next part of the conversation on better contact lens habits," says Dr. Kligman.

"If they're really motivated, then you should recommend they stay out of contacts for now, treat any ocular surface disease or dryness and re-evaluate in a couple of months to see if that surface is improving and becoming more regular and more appropriate for LASIK or PRK," he continues. "If they don't necessarily have any of the irregular curvature but might be on the thinner side or have a very high prescription, then I would be pushing the conversation more towards PRK. I tend to be on the more conservative side. For me, usually anything over 6 D of myopia and usually even with an average cornea, I'll lean towards PRK. It just seems safer and we're not pushing the boundaries of LASIK safety when it comes to the PTA (percent tissue altered)."

Dr. Dell says there has been some success in cross-linking for patients with keratoconus. "There are patients who come in seeking refractive surgery who have either indications of forme fruste keratoconus or outright keratoconus, and those patients are shifted toward corneal collagen cross-linking," he says. "We've successfully treated some patients with FFKC or even outright keratoconus with cross-linking and then observed them over a period of time and then very cautiously performed PRK on them in an off-label capacity. This has to be done very cautiously and with the understanding that this is an experimental and not FDA-approved method of using lasers."

As mentioned earlier, it's common for patients to assume they'll be getting LASIK since they had a friend or family member get it, not realizing there are other options. "I really lay out the pluses and minuses of both LASIK and PRK, even if they do qualify for LASIK, just so that they're fully informed and understand what each procedure means and what healing is involved for each and I can always point to the fact that 'Yes, it might take longer to get there with PRK, but ultimately, all of the literature shows that the results of PRK are equivalent to LASIK in the long term.' And so, I can kind of soften the blow if I don't think that they qualify for LASIK," Dr. Kligman says.

Ideal candidates for LVC are younger, in their 20s, who can have long-lasting results until their 40s when they may need reading glasses, says Dr. Kligman. "Especially someone in the -4 or -5 range who really cannot see much at all without their glasses or contacts, they seem to get the biggest bang for their buck. However, we do have a good number of people in their 60s and sometimes in their 70s who are interested in LASIK. In that case, if there's an early cataract, I don't like to encourage LASIK just because of the much shorter duration of the effect and especially for people who are hyperopic and don't qualify for medically necessary cataract yet, they are fantastic candidates for clear lens exchange. So that's a good way to steer the conversation for someone who might otherwise be disappointed that they can't get LASIK."

Dr. Doane does very few LASIK procedures, instead leaning on the benefits of SMILE. "I do very little LASIK at this point because almost everybody is a candidate for SMILE," Dr. Doane says. "If someone is a candidate for LASIK, they may very well be a candidate for SMILE. Situations in which they wouldn't be candidates is if we can't enter that prescription into the laser. Right now in the U.S. the maximum amount of astigmatism we can treat with SMILE is 3 D. Anybody above 3 D of astigmatism is going to get LASIK. And, obviously right now with SMILE, we're just treating simple myopia. In my practice, the people who end up getting LASIK would be anybody with mixed astigmatism, anybody with higher amounts of astigmatism. The reason we end up doing SMILE is our enhancement rate is about one-third of what it is with LASIK. Not that we have huge numbers of LASIK enhancements, we just have a lower enhancement rate with SMILE than we do with LASIK."

During the decision-making process, refractive surgeons need to keep the golden rule in mind, continues Dr. Doane. "I would only do unto a patient that which I would do to myself or a family member," he says. "If I see things that set off red flags to avoid lamellar surgery, such as abnormal corneal anatomy, abnormalities in the epithelial thickness or shows signs of FFKC, then I am going to tell my patients I'm not doing it, and their alternatives are PRK, ICL or nothing."

Dr. Kligman thinks similarly. "If they were my sibling or my best friend, I'd want the safest procedure for them while being equally effective one way or the other," he says. "Of course I would prefer to do LASIK for the patient and for myself when it comes to chair time and the rapidity of healing, but I'm not going to do anything that I wouldn't do to a family member." ◀

1. Belin MW, Kundu G, Shetty N, Gupta K, Mullick R, Thakur P. ABCD: A new classification for keratoconus. Indian J Ophthalmol 2020;68:12:2831-2834.

REFRACTIVE PROCEDURES IN THE PIPELINE

Refractive surgery researchers and companies are looking towards procedures similar to SMILE in an effort to focus on lenticular procedures' strengths.

CATLIN NALLEY
CONTRIBUTING EDITOR

Refractive technology continues to evolve, offering more options as well as the potential for improved patient outcomes. Small incision lenticule extraction, which received FDA approval in 2016, is a safe and effective procedure that achieves a refractive change by creating a lenticule-shaped piece of tissue with the VisuMax femtosecond laser (Carl Zeiss Meditec) and then removing it from the cornea with forceps rather than making a flap and ablating tissue like LASIK. Today, there are a number of new procedures in development that aim to improve upon this approach. Here, surgeons share their experiences with these new refractive surgery techniques while also discussing how they compare to currently available options and the potential impact on ophthalmic practice.

Small-Incision Lenticule Keratomileusis (SILK)

SILK—a surgical procedure developed by Johnson and Johnson Vision—uses a new femtosecond laser (Elita) to treat myopia and compound myopic astigmatism by removing a thin lenticule of stromal tissue from the cornea.

The procedure, which uses a technique similar to SMILE, can treat patients with myopia and compound myopic astigmatism with up to 10 D of myopia and up to 5 D of astigmatism, according to Edward E. Manche, MD, a professor of ophthalmology and director of the Cornea and Refractive Surgery Service at Stanford University School of Medicine.

Internationally, SILK has been tested in India and Singapore with positive results. The Elita femtosecond laser system received CE Mark approval in March.[1] This procedure isn't approved in the United States; however, the FDA trial was recently initiated by Dr. Manche and colleagues. While data is limited, preliminary results are promising, with most patients experiencing excellent vision in the early postoperative period similar to results seen with LASIK surgery, he notes.

While discussing how SILK stands out compared to currently available options, Dr. Manche notes that this new procedure has a number of unique differences when compared to SMILE.

"The SILK procedure on the Elita femtosecond laser allows adjustment for centration over the entrance pupil as well as cyclotorsion control on the operating screen," he explains. "It's a very high-speed laser which operates at 10-MHz level compared to the kilohertz levels of current femtosecond laser systems used for SMILE surgery.

"The Elita system," Dr. Manche adds, "also uses low energy level settings (less than 50 nanojoules) which produces a very smooth lenticule. In addition, the Elita utilizes overlapping spots, which allows for minimal dissection of the lenticule enabling nearly dissection-free removal of the lenticule."

Patients who undergo lenticule creation have a similar experience as those who receive LASIK flap creation performed using the Intralase iFS 150 femtosecond laser, explains Dr. Manche while noting that the

This article has no commercial sponsorship.

Dr. Manche is a consultant for Avedro, Carl Zeiss Meditec and Johnson & Johnson Vision. **Dr. MacRae** has an equity interest in Clerio Vision. **Dr. Mehta** gives lectures for Zeiss, Ziemer, Leica, Santen and Moria. **Dr. Chu** is a consultant for Bausch + Lomb. **Dr. Pradhan** has no financial disclosures.

Elita femtosecond laser uses scleral-based suction similar to the Intralase.

"The patient will feel some pressure in their eye during lenticule creation. Once the SILK procedure is completed on the Elita femtosecond laser, the patient is repositioned under the microscope," he says. "The superior incision is opened, and lamellar dissection is performed on the anterior and posterior lenticule planes. In most cases, there's minimal dissection needed and the lenticule comes out very easily."

During the procedure, patients are very comfortable and don't experience any postoperative pain the first 12 to 24 hours. Dr. Manche reports that patients typically see quite well on postoperative day one and can return to normal activities the following day.

Dr. Manche and colleagues hope that the SILK surgical procedure will lead to even better outcomes than what is observed with the currently FDA-approved SMILE surgical procedure. "Having the ability to adjust for pupil centration as well as cyclorotation should, in theory, improve refractive outcomes," he notes. "In addition, the ease of lenticule removal with minimal dissection should, in theory, lead to faster recovery of vision at postoperative day one."

Laser-Induced Refractive Index Change (LIRIC)

This procedure, which is currently in development, is described as a minimally-invasive approach to refractive surgery, using a femtosecond laser by Clerio Vision. LIRIC is an incision-free procedure for correcting corneal refractive error, according to Scott MacRae, MD, at the University of Rochester. "Unlike refractive surgery, there's no ablation, epithelial debridement or flap cutting," he explains. "Also, because LIRIC doesn't require epithelial debridement or the instillation of any dopant drugs, such as riboflavin (as opposed to corneal cross-linking). This strategy could help minimize patient postoperative recovery times both with corneal and IOL treatments," suggests Dr. MacRae, who also notes that LIRIC would give clinicians a minimally invasive option to correct refractive error and do sequential treatments if a patient's refraction changes.

"Currently in ophthalmology, femtosecond lasers are primarily used to ablate or cut material, such as flap cutting in laser refractive surgery or crystalline lens dissection in cataract surgery," he says. "In these cases, every laser pulse acts as a miniature explosion, creating water cavitation bubbles, allowing the dissection of tissue."

He explains that LIRIC spares the corneal nerves, causes much less damage to keratocytes and leaves the topography of the cornea intact, and notes, "Instead of ablation, LIRIC uses much lower pulse energies to modify the tissue's refractive index. The change in refractive index is highly localized, like using a fine-point pen."

Most patients are candidates for LIRIC, according to Dr. MacRae. "Since the LIRIC procedure doesn't remove any tissue, patients with thin corneas, who otherwise would be poor candidates for laser refractive surgery, would stand to gain the most from this procedure."

Clerio is also developing LIRIC treatment directly to implanted IOLs in pseudophakic eyes. "About a third of post-cataract patients have some residual refractive error due to healing of the capsular bag and post-implantation IOL movement," Dr. MacRae explains. "LIRIC can correct those residual aberrations for an 'optical touch-up.'"

In their clinical and pre-clinical work to date, Dr. MacRae and colleagues haven't observed any induced inflammation or wound healing response. Post-treatment corneas were clear, had no scatter and no signs of inflammation. As noted earlier, LIRIC resulted in significantly less keratocyte cell death compared to fs-laser flap cutting and left the corneal nerves intact, according to histology studies.[2,3]

Treatment time for the first-in-human presbyopia treatment was approximately one minute. Dr. MacRae envisions that this will shorten to well below a minute as the technology matures.

Proponents say this procedure could be a game-changer for refractive surgery and help mitigate patient fears surrounding surgery. "We expect corneal LIRIC to address that limitation of laser refractive surgery," says Dr. MacRae. "In addition to widening the eligibility criteria to patients with thin corneas, because LIRIC doesn't remove tissue or change corneal curvature, we expect to see less impact of epithelial remodeling, and fewer instances of dry eye."

Dr. MacRae and colleagues are currently developing a near-infrared version of corneal LIRIC and are in the midst of pre-clinical testing in collaboration with an ophthalmic company. While this approach holds significant promise, Dr. MacRae acknowledges that there are formidable technical challenges when it comes to developing a femtosecond laser system for corneal LIRIC in the near infrared.

"To allow for LIRIC, rather than flap-cutting, the laser system has more stringent specifications around pulsewidth," he explains. "Developing clinical devices with ultrashort laser pulses is critical for LIRIC and requires careful engineering."

Dr. MacRae and his team are excited for the future of LIRIC and their ongoing efforts to develop techniques for both refractive surgery and post-IOL implantation touch-ups. "Outside of these areas, we're also working on advanced contact lens products where the LIRIC system will be used as a tool for embedding diffractive optical patterns into soft contact lenses," he says. "We have programs aiming to develop such lenses for better correcting presbyopia and a therapeutic lens for the more effective treatment of myopia progression."

Corneal Lenticule Extraction for Advanced Refractive Correction (CLEAR)

This femtosecond laser surgery is used to correct myopia with or without astigmatism. By using a low-energy laser, CLEAR maximizes precision with minimal tissue and side effects as well as less inflammatory response. The procedure, which is performed with the Femto LDV Z8 laser (Ziemer Ophthalmic Systems), received the CE Mark in April 2020 for the correction of -0.5 to -10 D of sphere and up to -5 D of cylinder.[4]

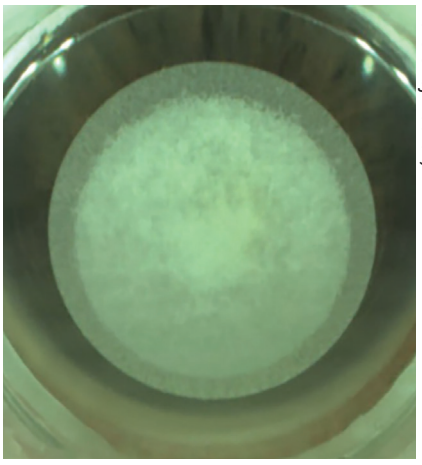
The CLEAR procedure is an optional software upgrade to the Z8 multipurpose laser, explains Professor Jod S. Mehta, BSc (Hons.), MBBS, PhD, FRCOphth, FRCS (Ed), FAMS, FARVO, Distinguished Professor in Clinical Innovation in Ophthalmology, SNEC. The laser platform can also be used for cataract surgery, corneal transplantation, pterygium surgery, tunnel and pocket creation for inlays and LASIK flap creation."

The Z8 laser is based on a low-energy (<100 nJ) high-frequency (up to 20 MHz) concept, according to Dr. Mehta and colleagues, "where the miniaturized scanning optic, integrated into the handpiece, and its high numerical aperture create highly focused laser pulses."[4]

Using a femtosecond laser, CLEAR creates a refractive lenticule that's then removed through either one or two small incisions in the cornea, depending on surgeon experience, notes Dr. Mehta. He refers to it as a "second-generation procedure," that differs from the established lenticule procedure.

These differences, according to Dr. Mehta, include lower energy, a smaller machine which makes it easy to handle, lenticule creation/centration and cyclotorsion control that's customizable from the laser screen, and decreased patient discomfort due to the procedure's speed.

"Following topical anesthesia, the patient is asked to fixate on a red target during applanation," he explains. "After this is performed, there's little else for the patient to do apart from relax. The lenticule procedure is fully customizable with the suction on, hence there's no need for the patient to be actively involved in the refractive procedure."



Kishore Raj Pradhan, MD

Figure 1. SmartSight is a minimally invasive lenticule extraction procedure developed using the Schwind ATOS femtosecond laser. Pictured here is the laser making the refractive cut.

Dr. Mehta says the CLEAR procedure may be a better option for patients prone to dry eye or those who aren't candidates for LASIK. It also provides a faster visual recovery with most patients returning to their normal routines just a few days after the procedure.

As with any new procedure, especially a refractive one, Dr. Mehta acknowledges that you want to approach it with some caution. "There will always be some optimization of the laser that's required," he says. "Our experience has been positive so far. We've had some excellent results and now we're working to improve on this promising start. With so many different procedures, it is an exciting time to be a refractive surgeon."

SmartSight

This minimally invasive lenticule extraction procedure, powered by the ATOS femtosecond laser (Schwind eye-tech-solutions), can be used to treat myopia as well as astigmatism. While not FDA approved, this laser platform received CE approval in 2020.

The SmartSight procedure creates a predefined lenticule in the intrastromal tissue of the cornea and makes small peripheral incisions in the top corneal layer for lenticular access. This approach uses no corneal flap and there's no laser ablation.[5]

Additionally, SmartSight includes an eye tracking system, with pupil recognition and cyclotorsion compensation. "It uses very low energy and has asymmetric laser patterns that make it very easy to dissect, and it also has the least corneal swelling postop," notes Kishore Raj Pradhan, MD, medical director, Matrika Eye Care Center, Kathmandu, Nepal.

Research has demonstrated that myopic astigmatism correction with SmartSight resulted in good efficacy, safety, predictability and visual outcomes in the first three months of follow-up. The study authors reported that spherical equivalent correction within ±0.5 D was achieved in 62 eyes (60 percent), and cylindrical correction in 90 eyes (87 percent).[6] Additional research by Dr. Pradhan and colleagues found that patients treated with SmartSight lenticule extraction had positive outcomes at 12-months of follow-up.[7]

Dr. Pradhan has experienced the evolution of SmartSight firsthand, performing more than 1,600 SmartSight procedures already. He notes a number of strengths, including less dryness postoperatively, a strong cornea postop and very good results. "The ATOS is still evolving and the surgeries are getting faster and easier every day," he says.

Ongoing Advances

Another interesting development is the initiation of a trial evaluating the safety and efficacy of the Technolas Teneo excimer laser for LASIK vision correction surgery for hyperopia with astigmatism (Bausch + Lomb).

The first patient was recently en-

(Continued on p. 68)

HOW TO MANAGE POSTOP INFLAMMATION

A simplified treatment regimen may be able to improve patient compliance, surgeons say.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Imagine taking months to build a house—painstakingly selecting everything from the flooring and furniture to the light fixtures and drawer pulls—only to have fire sweep through and gut the place. This is a lot like postop inflammation after cataract surgery; you did everything right and got a good result, but now the inflammation threatens all of your hard work. While most inflammation after routine cataract surgery is minimal and resolves relatively quickly, persistent inflammation after cataract surgery is a complication that's been reported in 0.24 percent to 7.3 percent of cases.[1] In this article, surgeons discuss the ways they use to keep inflammation at bay.

Risks for Postop Inflammation

In a study conducted at the Montefiore Medical Center in New York, persistent inflammation after complex cataract surgery was observed in nine of 156 cases (5.7 percent) regardless of gender, age, ethnicity or intraoperative use of iris-retention devices, and it was best predicted by the use of a prostaglandin analogue at the time of surgery.[1]

According to Andrew A. Kao, MD, some cataract patients are more prone to developing postop inflammation than others. "For example, patients with a history of uveitis or diabetes are more at risk for postoperative macular edema," says Dr. Kao, who is in practice in Bakersfield, Calif.

Los Angeles' Uday Devgan, MD adds that more inflammation occurs in patients with longer duration of surgery, dense cataract that requires more ultrasonic energy to break up, more fluidic flow during surgery, complications during surgery, retained lens material, younger age (younger patients have more inflammation typically than older patients), and a genetic variation of inflammatory response.

Michael Saidel, MD, who is in practice in Petaluma, California, agrees. "Cataract surgery itself causes inflammation," he notes. "Another cause of runaway inflammation is that the postoperative anti-inflammatory management was insufficient, whether because of patient non-compliance or surgeon management. Additionally, it can be due to residual lens material left behind after the cataract surgery and lodged in the sulcus, in the angle, or elsewhere in the eye. It can also be due to complications from cataract surgery."

Inflammation after Routine Surgery

Surgeons say they have their own preferred methods of delivering corticosteroids or nonsteroidals postop.

Dr. Devgan's treatment regimen for routine cataract surgery is topical steroid drops, usually prednisolone acetate, three times a day for two weeks.

"One pearl is to inject a little preservative-free triamcinolone (0.5 mg) into the anterior chamber at the end of the case to quickly quell inflammation in the immediate postop period," Dr. Devgan says.

Drs. Saidel and Kao have switched from commercially available drops

This article has no commercial sponsorship. **Drs. Devgan, Kao** and **Saidel** do not have a financial interest in any of the products mentioned.

to a compounded medication in an effort to improve patient adherence to therapy and to decrease patient costs. "For routine patients with no history of uveitis or any other ocular pathology, I use a combination of prednisolone, gatifloxacin or moxifloxacin antibiotic, and an NSAID, typically bromfenac, in combination," Dr. Saidel says. "They're compounded and used three times a day for approximately 3.5 weeks."

Dr. Kao's practice also uses a compounded fluoroquinolone, steroid and NSAID combination. "We tell patients that the medications cost a flat fee of $40, and the compounding pharmacy sends the medication directly to the patient's house, so there are no issues of patients neglecting to get the drops," he says. "It also enabled us to simplify our drop regimen. Instead of instilling each drop three or four times a day, we simplified it to where they can just instill this compounded drop twice a day for two weeks and then once a day for two weeks. This has made patients a lot more adherent to treatment, and we haven't seen any increase in rebound iritis or macular edema using this regimen."

Using three separate medications can be confusing for patients, especially elderly patients. "Even with our simplified regimen, some patients still have questions," Dr. Kao says.

Because non-compliance is such a significant issue in this patient population, researchers are studying new ways to deliver medications. One example is a liposomal drug delivery system that's currently in a Phase I/II trial.[2] The study concluded that liposomal prednisolone phosphate, administered as a single subconjunctival injection intraoperatively, can be a safe and effective treatment for post-cataract surgery inflammation.

All patients in this trial received a single injection of subconjunctival liposomal prednisolone phosphate for the treatment of postop inflammation. The primary outcome measure was the proportion of eyes with an anterior chamber cell count of zero at one month postop. Five patients were enrolled in this study, and the percentage of patients with anterior chamber cell grading of zero was zero percent at day one, 80 percent at week one, 80 percent at one month, and 100 percent at month two after cataract surgery. Compared to baseline, mean laser flare photometry readings were significantly elevated at week one after cataract surgery (48.8 ±18.9) decreased to 25.8 ±9.2 at month one and returned to baseline by month two (10.9 ±5.1).[2] There were no ocular or non-ocular adverse events.

Non-Routine Patients

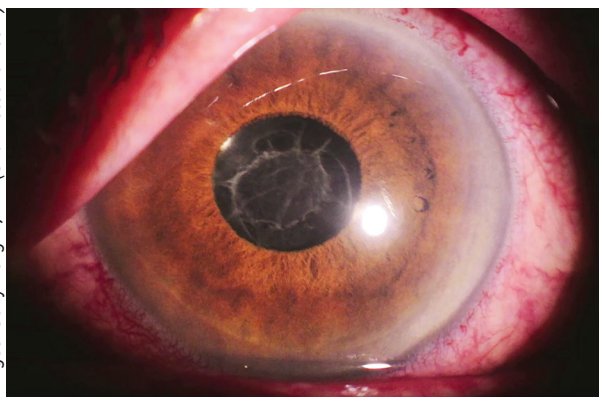
Patients who experience significant amounts of inflammation fall into one of two categories: those with pre-existing conditions who are expected to have issues with inflammation and those who simply don't respond to initial treatment.

According to Dr. Saidel, patients in these two categories are handled very differently. "If I have a patient with uveitis, I want to reach a level of quiescence of uveitis for three months prior to surgery," he says. "This typically means a zero-tolerance policy for anterior chamber inflammation and inflammation in the rest of the eye. The physician should be checking the anterior chamber in a darkened room, under high power, ensuring that there are no cells in the anterior chamber for three months prior to the surgery. Whatever it is that got the patient into this remission should be continued through the preoperative and postoperative period."

Prior to surgery, he'll start these patients on topical steroids and topical NSAIDs for a minimum of three days immediately preoperatively. "I will usually, although not universally, use systemic steroids starting three days prior to the surgery and for a minimum of a week after, although frequently I'll taper those over the course of a month," he says. "In addition, I'll take extra measures, including a stronger steroid drop, like difluprednate, as opposed to my usual combo drop, as well as using intracameral slow-release dexamethasone, if that's appropriate. In some patients, I'll also perform a posterior sub-Tenon's or periocular steroid injection, and steroids are titrated based on patients' need and their risk of elevated intraocular pressure, as well as concerns of elevated blood sugar in diabetics or any patient who may suffer from those conditions. So, the group of patients with known intraocular inflammation are managed very differently than patients who have a surprise intraocular inflammation."

For those with unusual or resistant inflammation with no pre-existing conditions, Dr. Devgan increases the dosing of his regimen to six times per day, and he will sometimes consider locally injected steroids. "Patients rarely require systemic steroids," he explains.

Dr. Kao adds that he'll switch patients who don't respond to initial therapy to a commercially available drop, like prednisolone or difluprednate, and increase the frequency of the drop. "If I expect a patient to have more inflammation than usual,

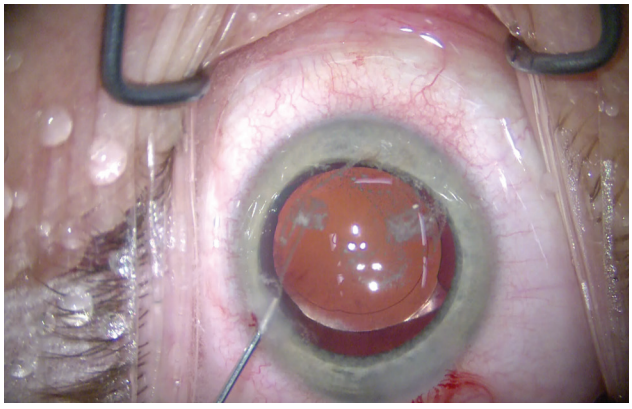


Images: Uday Devgan, MD (Cataractcoach.com)

A strong inflammatory response after surgery.

like someone with a history of uveitis, then I'll treat him or her preemptively with a commercially available drop preoperatively so that we try to quiet down any inflammation before it starts."

Dr. Saidel tailors treatment of these patients based on the cause. "If the cause is a complication of surgery, treatment is going to be different than someone who has just a simple rebound iritis," he says. "The most common postoperative inflammation we see is rebound iritis, which is typically managed in my practice with topical steroids. I'll sometimes do a systemic work-up for uveitis in the patient who doesn't respond as expected to typical topical treatment."



Triamcinolone being injected into the anterior chamber.

According to Dr. Saidel, the best way to prevent postoperative inflammation is to treat it before it starts. "And, for patients who are at risk, being aggressive with localized immunosuppression has been shown to produce better outcomes," he says. "So, prevention is the key. Performing a good examination of the anterior chamber in a darkened room is crucial to quantifying how much inflammation a patient really has."

He adds that, for the patient who has a history of uveitis and prior intraocular inflammation, it's important to perform OCT and a thorough exam of the retina prior to surgery. "In a patient who has unexpected postoperative inflammation, examining the posterior segment, as well as performing an OCT, is important to rule out other pathologies, including cystoid macular edema," Dr. Saidel says. "In addition, in patients with posterior pathologies, I'll refer to a retina specialist."

Intraoperative "Dropless" Regimen

Many ophthalmologists are moving to intraoperative medication therapy to address the noncompliance issue. "The biggest argument for this is patients being unable to stick to the drop regimen," says Dr. Kao. "Many ophthalmologists are prescribing three drops that are being used multiple times a day. It's too confusing for patients. In my practice, instead of going completely dropless, we switched to a combined drop treatment, which has been really beneficial for our patients."

He says that his practice hasn't moved to dropless surgery, due to concerns about side effects, as well as cost. "We haven't seen the need to switch over because we have a postop drop regimen that works and that patients are relatively adherent to," Dr. Kao explains. "Dropless regimens can result in floaters for weeks after surgery, which can be undesirable for patients undergoing refractive cataract surgery. Additionally, cost of the dropless medications has to be considered if you own your own surgery center. However, in the future, if there are commercially available intraoperative medication regimens that are available and more affordable, we would consider switching. Right now, we haven't found dropless cataract surgery to be necessary for our patients."

Comparing Treatments

A recent study conducted in Denmark investigated whether a combination of topical nonsteroidal anti-inflammatory drugs and steroids were superior in controlling early postoperative inflammation after cataract surgery compared with topical NSAIDs alone and with dropless surgery where a sub-Tenon's depot of steroid was placed during surgery.[3] The study found no differences between groups randomized to NSAID monotherapy or combination of NSAID and steroid in controlling early inflammation after cataract surgery, but sub-Tenon's depot of dexamethasone was less efficient. Initiating prophylactic drops prior to surgery didn't influence early postoperative anterior chamber inflammation.

In this study, 456 patients were randomized to one of five regimens: ketorolac and prednisolone eyedrops combined either preoperatively (control group) or postoperatively; ketorolac monotherapy either preoperatively (control group) or postoperatively; or sub-Tenon's depot of dexamethasone (dropless group). All drops were used until three weeks postoperatively, starting three days preoperatively in the preoperative groups and on the day of surgery in the postoperative groups.

Flare increased significantly more in the dropless group compared with the control group that received a steroid and NSAID combination preoperatively. Intraocular pressure decreased in all groups but decreased significantly less in groups receiving prednisolone eyedrops both preoperatively and postoperatively compared with NSAID monotherapy and dropless groups. Compared with the control group, no differences in postoperative visual acuity were observed. ◀

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Optic Disc Hemorrhage: What Next?

A glaucoma specialist shares how to manage patients with bleeding nerves.

LUIS O. SILVA, MD
NEW YORK CITY

Nowadays, most glaucoma treatment and management decisions are based on OCT, RNFL and visual field data, with artificial intelligence expected to supplement our progression detection capabilities in the future. In addition to these imaging modalities and future algorithms, checking for the presence of optic disc hemorrhage can provide information about a patient's disease state and likelihood of progression.

Several studies, including the Ocular Hypertension Treatment Study,[1] the Early Manifest Glaucoma Trial,[2] the Collaborative Normal-Tension Glaucoma Study[3] and others[4] confirm that patients with disc hemorrhages are at high risk for progression. It's important to examine patients' optic nerves, even if the patient has just come in for a quick pressure check.

Disc hemorrhage is identified on examination of the optic nerve and/or on color fundus photographs. The OCT RNFL image doesn't identify disc hemorrhage. It may take time—as much as a year or more—to identify changes in the visual field or OCT RNFL due to disc hemorrhage.[5]

Here, I'll discuss how to proceed with a patient who has an optic disc hemorrhage.

What To Do

Optic disc hemorrhages are transitory and not every patient with a disc hemorrhage will progress, but it's an important warning sign that shouldn't be missed. The blood itself isn't as concerning as the underlying cause. When a patient presents with a disc hemorrhage, there are three things we must do:

1. Check if the IOP is within target range and assess fluctuation and compliance. Is the IOP consistently controlled? The pressures we measure in the office might not capture fluctuations in pressure that happen at other times of day and night, and it's not uncommon for patients to have poor compliance with their medications.

If one has access to at-home pressure monitoring tools such as the Triggerfish contact lens or iCare Home tonometer, these can provide a general idea of how stable the pressures are. One approach I like is checking the patient's intraocular pressure in a supine position. When patients are supine, their pressures are usually higher.[6]

2. Follow the area carefully. After a disc hemorrhage, monitor patients using alternating 10-2 and 24-2 visual fields and RNFL/retinal ganglion cell OCT. Follow the patient every three months or

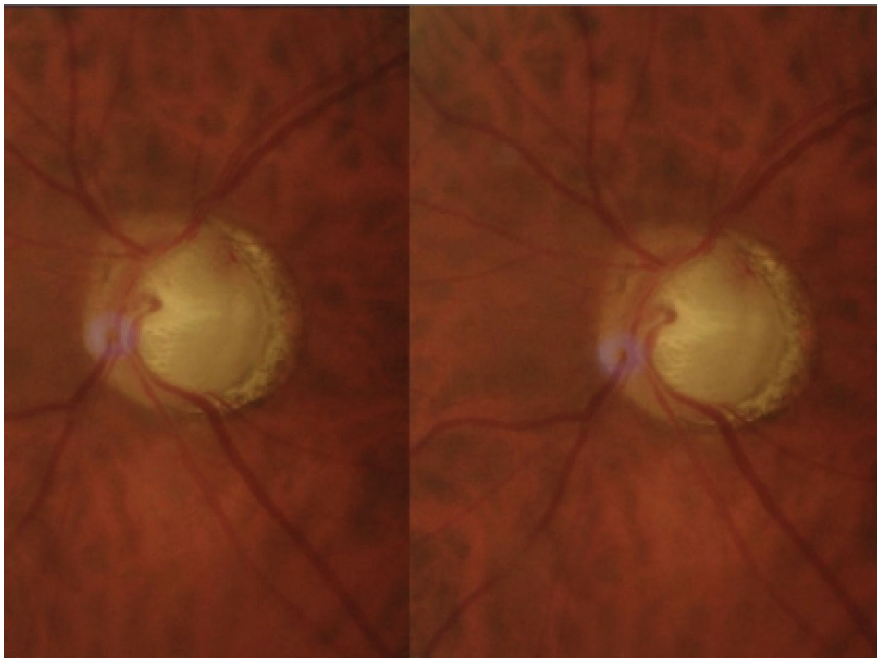

Figure 1. A disc hemorrhage in resorption (Case #1).

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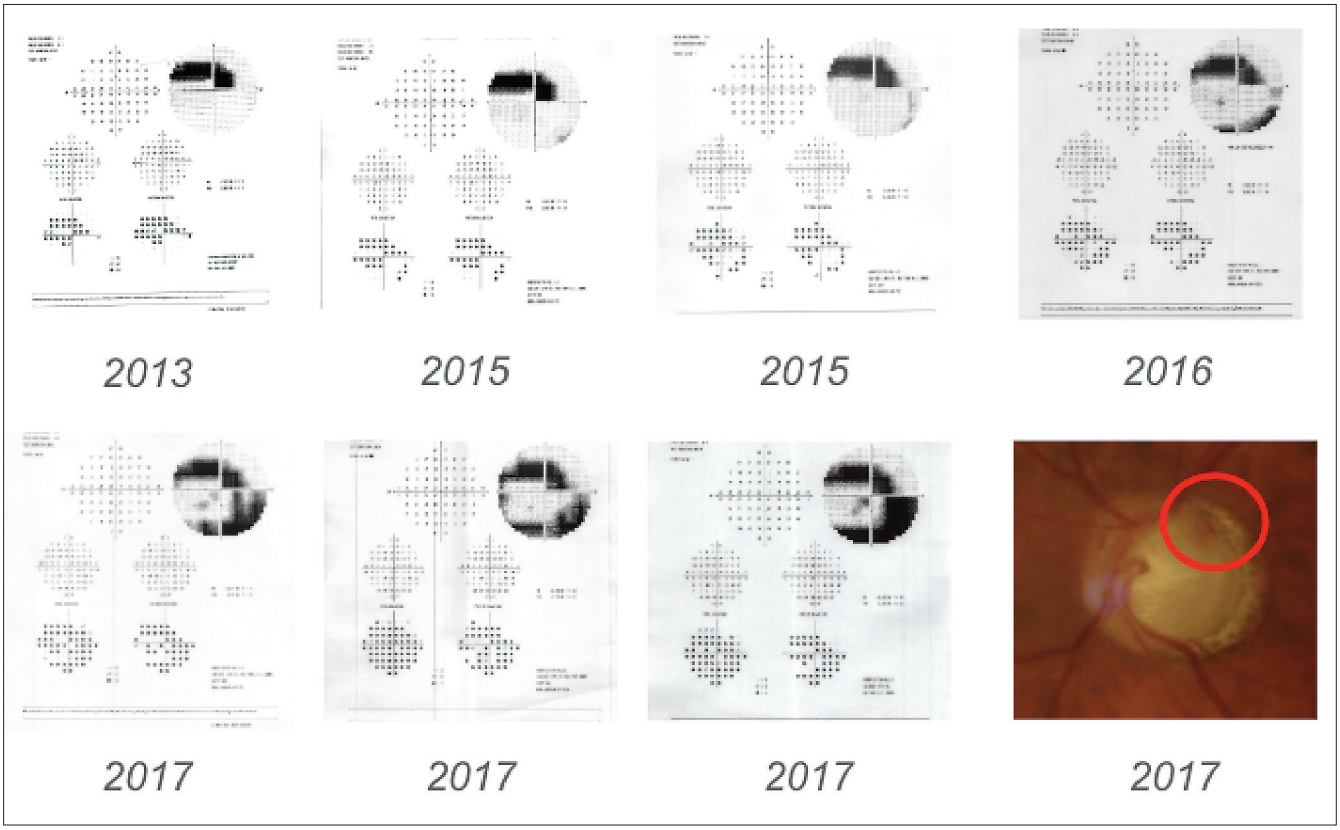

Figure 2. After a disc hemorrhage in 2017, the patient in Case #1 began to progress, demonstrating an arcuate defect on 10-2 visual fields. Pressures were stabilized following surgical intervention.

so and watch the areas where the disc hemorrhage occurred to ensure the patient isn't going to develop further progression in that area. It's key to use the 10-2 visual field to avoid missing early defects or small changes in the central visual field. If vision is poor, a size-five stimulus must be used.

3. Rule out other causes. Confirm there are no other IOP-independent risk factors for progression such as nocturnal hypotension or sleep apnea.[7,8]

Case #1

A patient with severe normal-tension glaucoma with pressures in the mid-teens started to progress after a disc hemorrhage in 2017 (*Figure 1*). He had previously undergone selective laser trabeculoplasty and used travoprost every night at bedtime, timolol 0.5% every day upon awakening in the morning and brinzolamide twice daily. He was allergic to brimonidine.

The patient was followed closely using 10-2 visual fields to confirm and document progression (*Figure 2*). Deep sclerectomy was performed to further lower the pressure to safer levels.

Case #2

This 83-year-old patient with severe pseudoexfoliation glaucoma and previous trabeculectomy began to develop disc hemorrhages in the same area in 2018. Between 2018 and 2020, we detected five disc hemorrhages superotemporally (*Figure 3*). Corresponding inferonasal spots started to appear in 10-2 visual fields.

Surgery was suggested, but the patient was hesitant to proceed as she was concerned about the risks associated to surgery. Based on careful monitoring, we determined that the progression was slow. Since progression was slow and she was concerned about possible surgical complications, we decided to maximize her medical treatment to further decrease intraocular pressures. So far, her glaucoma has been fairly stable, as demonstrated by the downward-trending IOP from the GPA analysis and by the RGC OCT, which is very useful for analyzing progression in severe glaucoma.

It's Not Always Glaucoma

Most of the time, disc hemorrhages in patients with glaucoma are related to the disease itself. These glaucomatous disc hemorrhages are flame-shaped and located adjacent to an area of a retinal nerve fiber layer defect. However, when the disc hemorrhage isn't flame-shaped, is broader or not related to a specific RNFL defect, we have to

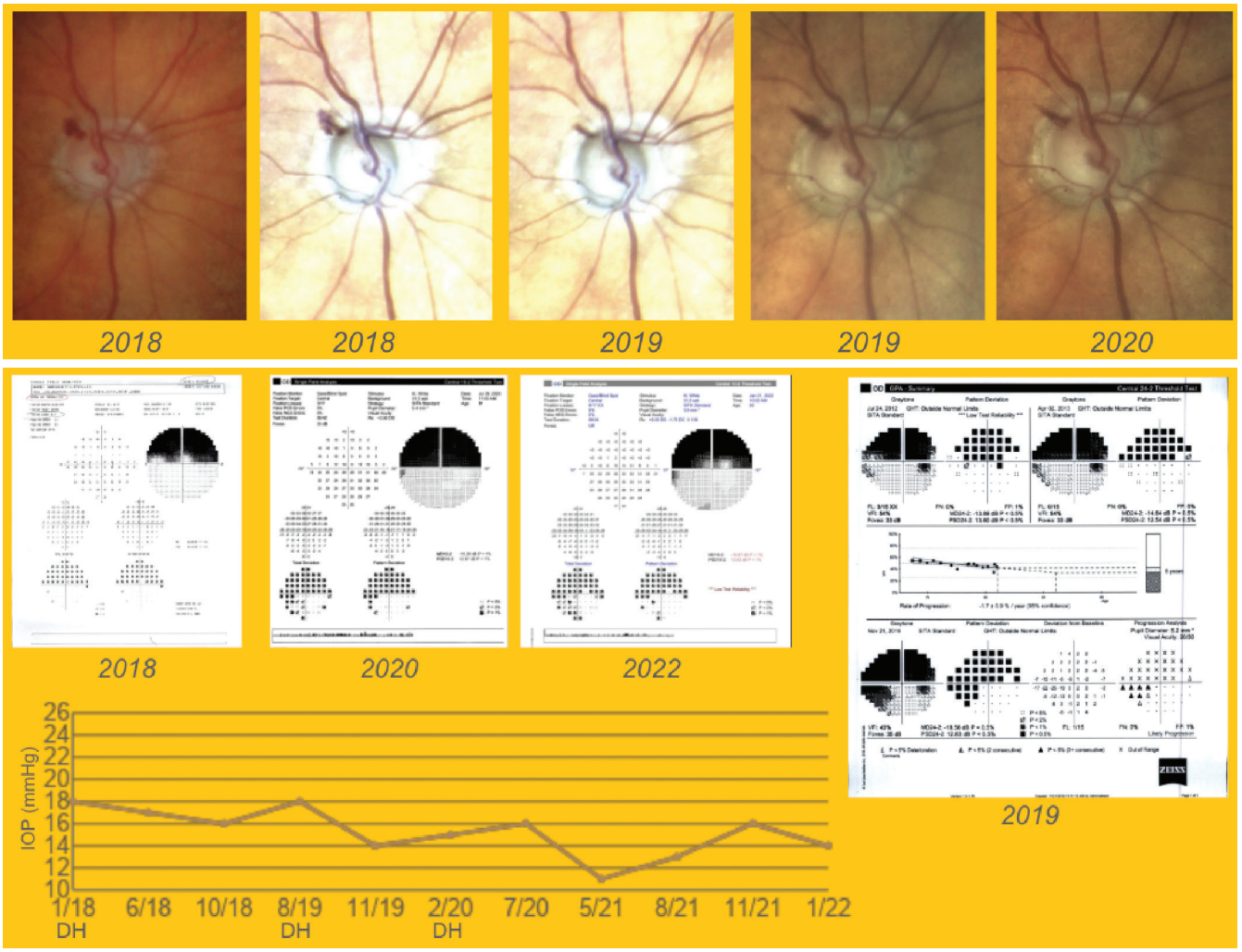

Figure 3. A patient in her 80s developed several disc hemorrhages over a two-year period in the superotemporal area (Case #2). Surgery was recommended, but the patient preferred to use maximal medical therapy, which was adjusted to further decrease IOP, and has remained stable. Some inferonasal spots were seen on the 2020 10-2 visual fields but IOP remained overall stable.

consider other causes.

Other causes of disc hemorrhage may include retinal diseases, ocular trauma, posterior vitreous detachment, and brain or optic nerve diseases; and systemic diseases such as hypertension, diabetes mellitus, hematologic disorders, migraine and systemic medications such as blood thinners.[9]

Most of the time, asking patients questions and using clinical data will help us make the diagnosis. For example, a posterior vitreous detachment is a common cause and patients will often say they've noticed a new floater. In patients with uncontrolled diabetes and diabetic retinopathy, we may see disc hemorrhages that are associated with other retinal findings. Blood discoloration may suggest coagulation problems, and migraines may lead to disc hemorrhage due to vasospasm.

Figure 4 shows an example of a broad superior disc hemorrhage that's not related to glaucoma. In this example, the patient was vitrectomized (so we ruled out PVD), asymptomatic and being followed for ocular hypertension. He was also using blood thinners. We concluded that blood-thinner use was the cause, which put him at a higher risk for disc hemorrhages or any retinal hemorrhages.

It's very important to perform a dilated fundus exam to rule out retinal causes such as branch retinal vein occlusions or central vein occlusions. Vein occlusions may cause more dramatic disc hemorrhages that are spread widely across the retina, unlike glaucomatous ones (*Figure 5*).

Normal Tension Glaucoma

Be vigilant in normal-tension glaucoma patients. These patients present more often with disc hemorrhages than patients with other glaucoma subtypes. It may be that these hemorrhages aren't solely pressure-related but could result from mechanical forces or vascular dysregulation. We know

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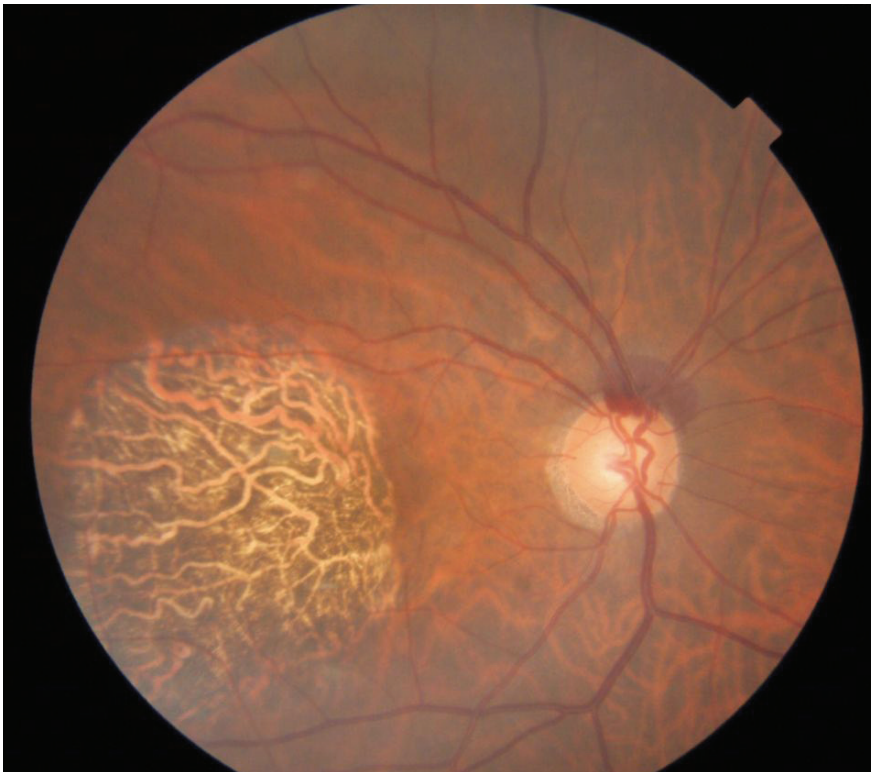

Figure 4. A broad, superior, non-glaucomatous disc hemorrhage. Glaucomatous disc hemorrhages are usually flame-shaped and located next to a retinal nerve fiber layer defect.

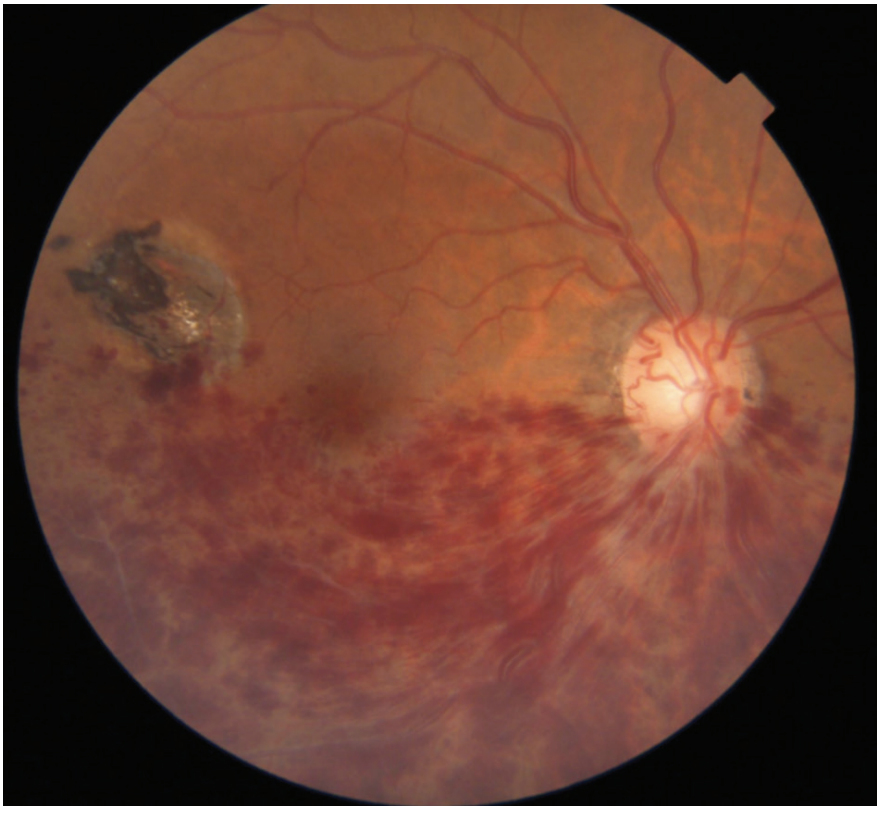

Figure 5. A branch retinal vein occlusion results in a more dramatic, widespread hemorrhage.

that normal tension glaucoma patients have a higher frequency of vascular dysregulation phenomenon,[10] and that it's more common among women, sometimes with a previous history of migraines or Raynaud's phenomena—both of which are also signs of vascular dysregulation.

In summary, optic disc hemorrhages associated with glaucoma are important warning signs of possible disease progression. Perform a thorough assessment, monitor the patient closely for progression and adjust treatment accordingly.

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Autoimmune Retinopathy: A Review

The signs and symptoms to be aware of, as well as the best courses of treatment to pursue.

THEODORE BOWE, MD,
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PHILADELPHIA

Autoimmune retinopathy (AIR) is a group of autoimmune degenerative retinal diseases characterized by stereotypical clinical, visual field, electrophysiologic and ocular imaging findings along with the presence of the circulating antiretinal antibodies (ARA).[1] Though AIR is rare, that makes it more important to be aware of the signs, symptoms and imaging findings associated with it, in order to make an accurate diagnosis when and if it presents. In this article, we'll review the epidemiology, diagnosis and treatment of AIR.

Epidemiology

AIR is thought to be a rare disease, constituting less than 1 percent of uveitis cases in one tertiary eye clinic.[2] AIR can be divided into two groups, paraneoplastic and non-paraneoplastic. Paraneoplastic AIR includes cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). Non-paraneoplastic AIR (npAIR) isn't associated with an underlying malignancy and is a diagnosis of exclusion.

Non-paraneoplastic AIR is more common than paraneoplastic AIR.[3] CAR is more prevalent than MAR.[3] The average age of symptom onset ranges from 55 to 65 years, with npAIR skewed towards younger patients compared to paraneoplastic AIR.[4–6] In patients with npAIR, comorbid autoimmune diseases are common, with a predilection for females.[4,7] The diagnosis of cancer typically predates the symptoms associated with CAR and MAR, but the timeframe is variable.[8] Rarely, ocular symptoms can precede the cancer diagnosis.[9] Therefore, it's necessary for the clinician to always remain suspicious. Numerous cancers have been associated with CAR, most commonly small-cell lung cancer.[10] Other cancers which have been reported to be associated with CAR include:

- breast;
- ovarian;
- endometrial;
- cervical;
- non-small cell lung cancer;
- lymphoma;
- colon;
- pancreatic;
- prostate;
- bladder; and
- laryngeal cancers.[10]

Pathophysiology

The pathophysiology of AIR is largely presumptive and is based upon the presence of circulating ARA, which are thought to target retinal antigens resulting in disease manifestation. In the case of paraneoplastic AIR, molecular mimicry is the proposed pathogenic mechanism behind the disease, wherein antibodies formed against tumor antigens are thought to cross-react retinal antigens, resulting in disease.[2] It's been postulated that ARA are cytotoxic, inducing cell death after internalization through caspase-dependent apoptosis.[11]

Numerous ARA have been identified in the literature.[1] The most commonly targeted protein of ARA in CAR is recoverin, a 23 kDa protein found in retinal photoreceptor cells.[4] Another well described target of ARA is enolase, a 48kDa enzyme found in ganglion cells, Müller cells, rods and cones.[4] Notably, AIR associated with anti-recoverin antibodies is associ-

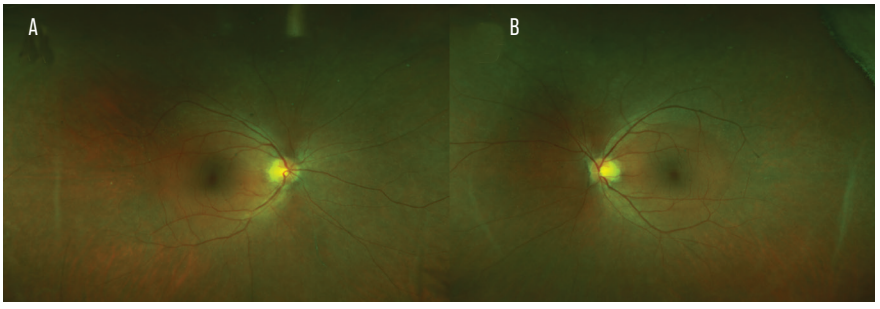

Figure 1. Ultra-widefield fundus photos of an autoimmune retinopathy patient's right (A) and left eyes (B) revealing diffuse bilateral but asymmetric retinal pigmented epithelial changes that spare the posterior pole along with arteriolar narrowing.

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Dr. Regillo is the director of the Retina Service of Wills Eye Hospital, a professor of ophthalmology at Thomas Jefferson University School of Medicine and the principle investigator for numerous major international clinical trials.
Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University. He serves on the Education Committee of the American Society of Retina Specialists and on the Executive Committee for the Vit Buckle Society, where he is also the vice president for academic programming.

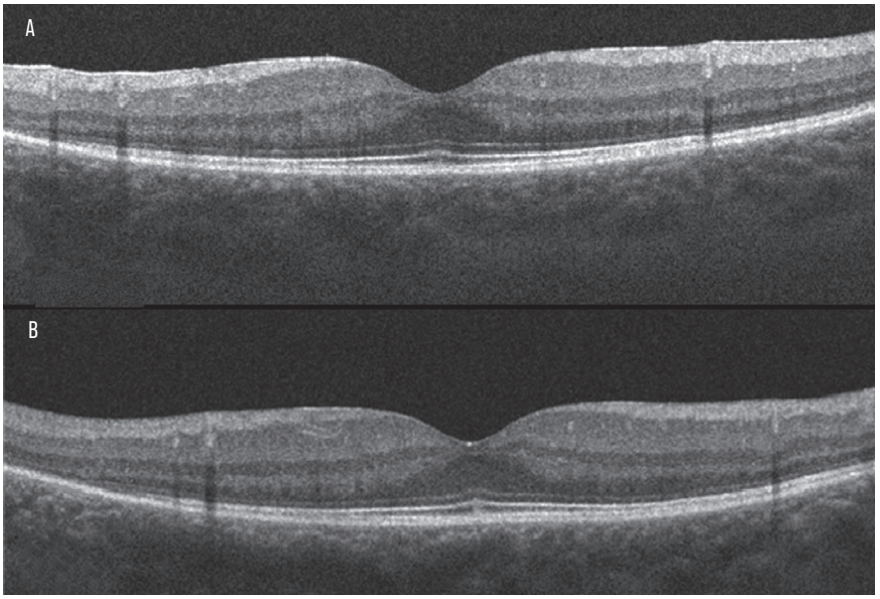

Figure 2. Optical coherence tomography of an autoimmune retinopathy patient's right (A) and left eyes (B) revealing peripheral loss of the outer retinal layers including the interdigitation zone, ellipsoid zone and external limiting membrane.

ated with worse outcomes compared to AIR associated with anti-enolase antibodies.[4]

Curiously, the presence of serum ARA has been detected in 42 percent of normal healthy controls.[12] ARA have also been detected in patients with various systemic autoimmune conditions, including Behçet's disease, systemic lupus erythematosus, inflammatory bowel disease and multiple sclerosis, all without ocular complications.[13–16] These findings suggest that the presence of ARA alone isn't pathogenic. Finally, ARA have also been detected in 10 to 51 percent of patients with retinitis pigmentosa.[17–19] RP and AIR present with similar clinical features, making clinical differentiation difficult. The high prevalence of ARA in patients with RP further blurs their differentiation. Interestingly, it's been hypothesized that RP cases with prominent intraocular inflammation may be part of an overlap syndrome between the two diseases,[19] especially when cystoid macular edema is present.[20]

Clinical Presentation and Diagnostic Imaging

The clinical findings of AIR are heterogenous and diverse.[1] Patients with AIR most commonly present complaining of subacute vision loss, peripheral visual field loss, flashing lights and/or night blindness.[2] Clinical examination in early disease may be unremarkable with a notable lack of intraocular inflammation.[2,7,10] This absence of clinical findings not only makes the diagnosis of AIR difficult but may also lead to a delay in diagnosis and treatment. As the disease progresses, advanced findings include narrowing of the retinal vasculature, retinal pigmented epithelial abnormalities, optic nerve pallor and mild vitreous cells (*Figure 1*).[2] AIR is usually bilateral but can be asymmetric.[2] Visual acuity is usually preserved until late disease.[2]

A constellation of diagnostic imaging findings can increase suspicion for a diagnosis of AIR, and in conjunction with clinical exam and positive ARA are key to making a diagnosis of AIR.

Spectral domain optical coherence tomography may be the most useful ancillary imaging test in the context of AIR. Multiple studies have shown that AIR is associated with progressive outer retinal loss, particularly of the ellipsoid zone that begins peripherally and initially spares the fovea (*Figure 2*).[21] Findings of outer retinal loss or EZ disruption may precede electroretinogram findings or ARA detection.[22–25] Initial treatments of AIR didn't appear to be associated with recovery of the EZ.[21,23–25] However, a recent report by our team has shown significant recovery of the EZ when npAIR with cystoid macular edema is treated with anti-interleukin 6 medications (tocilizumab or sarilumab).[26] Finally, OCT should be used to assess for cystoid macular edema, which is present in 24 to 66 percent of eyes[17,21] and is a biomarker of more severe and more progressive disease.[27]

Depending on the stage of disease, fundus autofluorescence (FAF) can reveal a diffuse or stippled hyperautofluorescent pattern throughout the posterior pole that initially spares the central macula. A parafoveal ring of abnormal hyperautofluorecence located between an area of normal autofluorescence inside the ring and hypoautoflourescence outside the ring

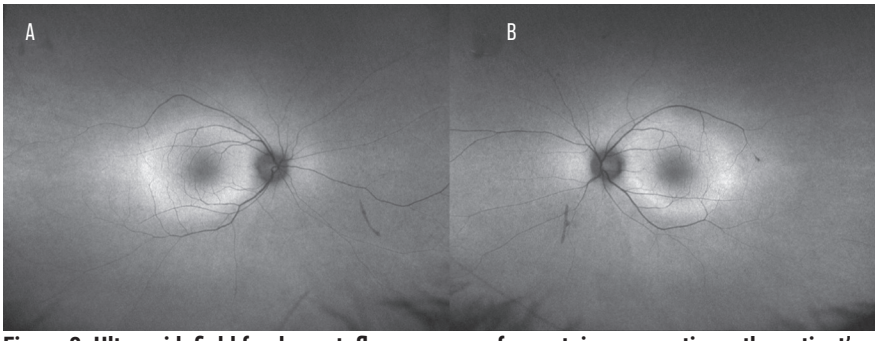

Figure 3. Ultra-widefield fundus autofluorescence of an autoimmune retinopathy patient's right (A) and left eyes (B) showing a ring of relative hyperautofluorescence in the macula surrounded by hypoautofluorescence in the periphery.

TABLE 1. SUMMARY OF THE RETROSPECTIVE CASE SERIES REPORTING TREATMENT OUTCOMES IN AUTOIMMUNE RETINOPATHY

Study	Patients	Diagnosis(es)	Molecular weight of ARA (kDa) at diagnosis	Treatment	Outcomes
Keltner 2001	62 patients	MAR	Not specified.	Oral, sub-Tenon's or intravenous corticosteroids; plasmapheresis, IVIG, azathioprine, irradiation or cytoreductive surgery of tumor	IVIG improved VA in one patient. IV corticosteroids and plasmaphoresis improved VA and VF in one patient. Cytoreductive surgery improved VF in one patient. Cytoreductive surgery and IVIG improved visual function in two patients.
Ferreyra 2009	60 eyes in 30 patients	npAIR, npAIR with CME, CAR	Not specified. All but 1 patient with early CAR were tested and positive for ARA	Triple therapy with cyclosporine 100 mg/day, azathioprine 100 mg/day and prednisone 20 to 40 mg/day. In cases without classic presentation or unavailable ARA, 1 or 2 sub-Tenon's methylprednisolone acetate injections (40 to 60 mg) were given as a trial. Patients who did not tolerate IMT were treated with periocular or intravitreal cortiosteroids	Overall, 21 of 30 patients (70%) improved in at least one metric: Six of six patients with CAR, seven of 13 (54%) with npAIR, and 8 of 11 (73%) with npAIR with CME. Five of 30 patients (17%) experienced improvement in VA. 15 of 30 patients (50%) had an expansion in VF, and six of 11 (55%) had resolution of CME.
Davoudi 2017	30 eyes in 16 patients	npAIR, CAR, MAR	22, 23, 28, 29, 30, 32, 34, 35, 36, 40, 41, 42, 43, 44, 45, 46, 50, 59, 60, 62, 65, 70, 71, 72, 82, 90, 91, 92, 94, 102	Primary outcome was assessing VA response to rituximab doses ranging from 1,000 mg every other week for two weeks to 375 mg/m^2 weekly for four weeks. However, most patients (14/16, 88%) were on concurrent IMT or receiving local corticosteroids, including: mycophenolate, cyclophosphamide, bortezomib, IVIG, IVT, and/or PSTK	There was a significant reduction in the rate of VA loss beginning at six months after rituximab initiation. There was no change in OCT CST or TMV. There was no change in ERG implicit times or amplitudes.
Bourdreault 2017	10 eyes in five patients	npAIR	23, 28, 33, 34, 36, 39, 40, 42, 45, 46, 55, 62, 64, 68, 72, 90, 92	Rituximab infusions ranging from a single dose of 1,000 mg to four infusions of 750 mg separated by one-week intervals. No patient was reported to be on concurrent therapy.	One patient showed response to rituximab with improved VF, VA and ERG amplitudes and implicit times. Two patients showed stability with no further decline in VA or ERG metrics. Two patients showed no response and had deterioration in VF, VA, and/or ERG metrics.
Maleki 2017	12 eyes in six patients	npAIR	22, 30, 32, 33, 34, 35, 40, 43, 45, 46, 48, 50, 62, 72, 76, 122	Rituximab infusions ranging from two doses of 1,000 mg one week apart to four infusions of 350 mg/m^2 separated by one-week intervals. Most patients (4/6, 66%) were on concurrent IMT, including cyclophosphamide and bortezomib.	VA was stable in 8/12 eyes (67%) and reduced in the remainder. VF was stable in 6/12 eyes (50%) and improved in 2/12 eyes (17%). ERG was stable or improved in 8/12 eyes (67%).
Deaner 2021	15 eyes in eight patients	npAIR with CME	20, 23, 29, 30, 31, 36, 40, 42, 44, 46, 48, 52, 58, 60, 62, 94, 96, 132, 200	Tocilizumab infusions 4 to 8 mg/kg every four weeks or tocilizumab or sariumab subcutaneous injections every week. Only two patients were on concurrent systemic therapy with mycophenylate.	There was a significant improvement in OCT CST and TMV. CME resolved in four eyes (25%). VA improved by two lines or greater in six eyes (40%). All nine eyes with progressive EZ integrity loss showed significant recovery of the EZ.

ARA = antiretinal antibodies, npAIR = non-paraneoplastic autoimmune retinopathy, CME = cystoid macular edema, CAR = cancer-associated retinopathy, IMT = immunosuppressive therapy, VA = visual acuity, VF = visual field, MAR = melanoma-associated retinopathy, IVIG = intravenous immunoglobulin, IVT = intravitreal triamcinolone, PSTK = posterior sub-Tenon's Kenalog, CST = central subfield thickness, TMV = total macular volume, ERG = electroretinogram, EZ = ellipsoid zone

has been reported as a characteristic finding in one small cohort with AIR (*Figure 3*).[24] It's been hypothesized that the hyperautofluorescent ring likely represents an abnormal collection of lipofuscin in the RPE due to enhanced outer segment turnover during apoptosis.[28] Using FAF to monitor disease progression and response to treatment has been suggested.[24]

Visual field testing typically reveals peripheral constriction (*Figure 4*).[2] However, central or paracentral scotomas are also possible.[2] Fluorescein angiography rarely shows leakage, but should be performed to rule out other possible etiologies.

There are no ERG findings that are diagnostic for AIR. ERG abnormalities have been reported in both full-field (ffERG) and multifocal electroretinogram (mfERG) including abnormal cone, rod and bipolar cell responses.[29] Full-field ERGs may be more sensitive in detecting abnormalities in patients with AIR compared to multifocal ERGs.[21]

ERG can be particularly useful in some presentations of AIR, particularly those with CAR, MAR or anti-enolase antibodies. CAR is most commonly associated with anti-recoverin antibodies and ERG typically shows abnormalities in the cone responses,[4,30] whereas MAR typically shows an electronegative waveform on ffERG.[6] Finally, AIR associated with anti-enolase antibodies have

been reported to have normal or near-normal ffERGs but very abnormal mfERGs.[1]

Work-up

As discussed previously, the presence of ARA isn't diagnostic for AIR as they are present in a significant portion of the normal population.[12] Rather, the presence of ARA in the setting of compatible clinical and diagnostic imaging is necessary for a diagnosis of AIR. The detection of ARA can be performed using a variety of laboratory techniques including immunohistochemistry (IHC), Western blot and enzyme-linked immunosorbent assay (ELISA).[1] In brief, IHC involves exposing normal donor retina tissues to the suspect patient's serum.[1] If ARA are present, they bind to the retinal antigens and then are counterstained with a fluorescent-tagged anti-IgG, allowing for identification using confocal laser microscopy.[1] Identification of ARA with Western blot involves separation of normal donor retina proteins by molecular weight using electrophoresis.[1] These separated proteins are then exposed to the suspect patient's serum.[1] Again, if ARA are present, they bind to the retinal antigens and are then counterstained for IgG for identification.[1] Finally, ELISA is a very sensitive laboratory technique which can be used to quantify the amount of ARA present using a colorimetric reaction and a spectrophotometer.[1] A majority of patients with AIR have serum ARA against more than one retinal antigen.[17]

Systemic evaluation to rule out cancer is imperative in any patient with clinical or imaging concerns for AIR. Computed tomography of the chest, abdomen and pelvis along with magnetic resonance imaging of the brain should be performed to survey for any evidence of malignancy. Further investigation can be co-managed with the patient's primary care provider and should include a thorough review of systems, complete physical examination, basic laboratory work-up, along with age and gender appropriate screening for colon, breast, gynecologic and prostate cancer. A full body skin check should be performed to assess for dermatologic malignancies, particularly melanoma.

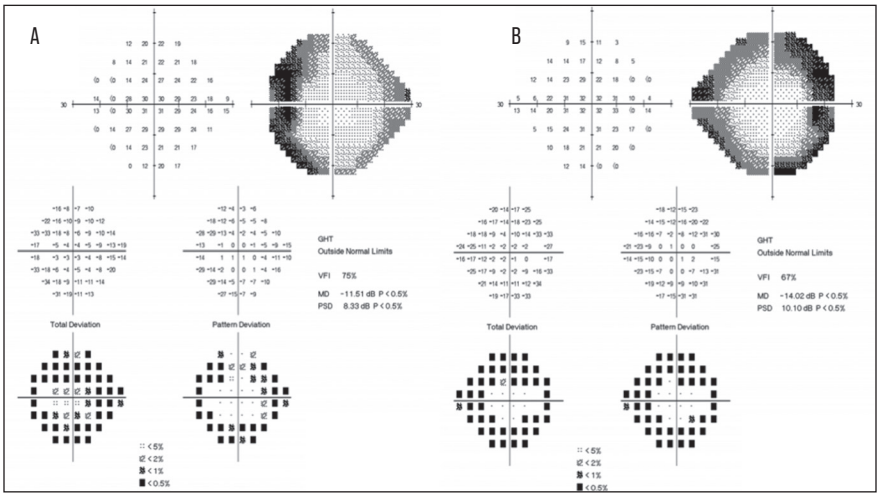

Figure 4. Automated static perimetry of an autoimmune retinopathy patient's right (A) and left eyes (B) revealing peripheral visual field constriction corresponding to her fundus photographs, optical coherence tomography scans and fundus autofluorescence in Figures 1-3.

The differential diagnosis consists of the following:

- retinitis pigmentosa;
- cone-rod dystrophy;
- toxic retinopathy;
- nutritional retinopathy;
- acute zonal outer occult retinopathy; and
- non-infectious and infectious uveitis syndromes.

The typical autoimmune retinopathy patient is a female in her mid 50's or 60's with no family history of retinitis pigmentosa or other inherited retinal dystrophies who presents with new onset flashes and peripheral visual field loss. If these symptoms are new in onset, funduscopic examination would likely appear normal. There should be limited, if any, intraocular inflammation. Review of possible toxic or nutritional deficits should be explored. If diagnostic imaging with OCT, FAF, ERG and visual field testing is consistent with findings reported in AIR, then you should perform ARA testing. If ARA are present, then be sure to perform a systemic evaluation for malignancy. If no malignancy is found, then you can assume a tentative diagnosis of npAIR.

Treatment

The management of AIR remains a challenge. High suspicion for a diagnosis of AIR allows for early diagnosis and treatment as therapy after widespread retinal degeneration occurs isn't helpful.[7,17] However, there is a lack of consensus in local or systemic treatment protocols for autoimmune retinopathy.[31]

If a diagnosis of CAR or MAR is made it is essential to eliminate or reduce the tumor burden through surgery, chemotherapy or radiotherapy, as indicated.[6,32,33] Decreasing the tumor burden is believed to decrease the amount of ARA production.[1]

Systemic immunosuppressive therapy is often administered given the suspected pathophysiology. Various treatments have been described in retrospective case reports and case series, including:

- local and systemic corticosteroids;
- cyclosporine;
- mycophenolate;
- azathioprine;
- rituximab;
- ipilimumab;
- sarilumab;
- tocilizumab;

- intravenous immunoglobulin; and
- plasmapheresis.[31]

Given the heterogenous nature of this ambiguous disease, perhaps it's unsurprising that the response to these treatments can be quite variable with most only slowing the progression of disease. However, we recently reported our success in treating npAIR with CME using the anti-interleukin 6 agents tocilizumab and sarilumab.[26] Not only did we see significant improvement in OCT central subfoveal thickness and total macular volume metrics with resolution of CME in 25 percent of eyes, but there was also a trend towards improved visual acuity, with 40 percent of eyes improving by two lines or greater.[26] Table 1 is a summary of the retrospective case series reporting treatment outcomes in autoimmune retinopathy.[6,7,26,34–36]

Patients are typically followed with serial functional and anatomic testing with repeat OCT and FAF at every visit and visual fields and ERGs every three to six months with the goal of stabilization or recovery. Several case reports have described a decrease in circulating ARA following treatment and have advocated quantification of ARA as a possible method of assessing response to treatment.[37–41] However, a recently published case series revealed no correlation between the quantitative change in ARA and clinical activity, suggesting that quantitative measurement of ARA shouldn't be used in making management decisions.[42]

In conclusion, autoimmune retinopathy remains both a diagnostic and a management challenge. The ophthalmologist must remain alert and suspicious for this occult and heterogenous disease. Multimodal imaging may help to identify subtle signs, and in the setting of positive ARA make a diagnosis of AIR. Malignancy must be ruled out prior to initiating local or systemic immunosuppressive therapy. Both the patient and physician must be aware of the uncertain disease prognosis and that response to therapy is variable. ◀

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Diabetic Retinopathy and Machine Learning

Investigators created and validated code-free automated deep learning models (autoML) for diabetic retinopathy classification from handheld-camera retinal images.

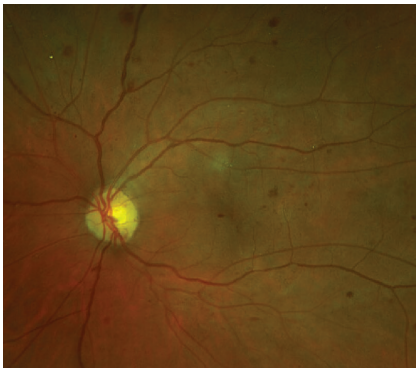
A total of 17,829 de-identified retinal images from 3,566 eyes with diabetes acquired using handheld retinal cameras in a community-based DR screening program were included.

AutoML models were generated based on previously acquired five-field (macula-centered, disc-centered, superior, inferior, temporal macula) handheld retinal images. Each individual image was labeled using the International DR and diabetic macular edema classification scale by four certified graders at a centralized reading center under oversight by a senior retina specialist. Images for model development were split 8-1-1 for training, optimization and testing to detect referable DR [(refDR), defined as moderate nonproliferative DR, or worse or any level of DME]. Internal validation was performed using a published image set from the same patient population (n=450 images from 225 eyes). External validation was performed using a publicly available retinal imaging dataset from the Asia Pacific Tele-Ophthalmology Society (n=3,662 images).

Main outcome measures included area under the precision-recall curve (AUPRC), sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV), accuracy and F1 scores.

Here are some of the findings:

- RefDR was present in 17.3 percent of the training set, 39.1 percent of the internal validation sets and 48 percent of the external validation sets.



- The model's AUPRC was 0.995 with a precision and recall of 97 percent using a score threshold of 0.5.
- Internal validation revealed the following scores:
  - — SN: 0.98 (CI, 0.937 to 0.995);
  - — SP: 0.96 (CI, 0.884 to 0.99);
  - — PPV: 0.98 (CI, 0.937 to 0.995);
  - — NPV: 0.98 (CI, 0.937 to 0.995);
  - — Accuracy: 0.97 (CI, 0.937 to 0.995); and
  - — F1: 0.96 (CI, 0.937 to 0.995).
- External validation revealed the following scores:
  - — SN: 0.94 (CI, 0.929 to 0.951);
  - — SP: 0.97 (CI, 0.957 to 0.974);
  - — PPV: 0.96 (CI, 0.952 to 0.971);
  - — NPV: 0.95 (CI, 0.935 to 0.956);
  - — Accuracy; 0.97 (CI, 0.935 to 0.956); and
  - — F1: 0.96 (CI, 0.935 to 0.956).

Investigators wrote that the findings validated the accuracy and feasibility of code-free automated machine learning models for identifying referable diabetic retinopathy developed using handheld retinal imaging in a community-based screening program. They added that the use of automated machine learning may increase access to similar models that may be adapted for specific clinical programs.

Ophthalmol Retina 2023; Mar 14. [Epub ahead of print].
Jacoba CMP, Doan D, Salongccay RP, et al.

Visual Impairment after Anti-VEGF Injections

Intravitreal anti-VEGF injections are the current standard of care for treating neovascular age-related macular degeneration, but vision loss still occurs in some patients. Researchers believe that the vision loss affecting this small subgroup of patients may be related to the number of intravitreal injections they receive.

Investigators conducted a retrospective, observational study analyzing patients who experienced sudden visual decline, defined as a loss of ≥15 ETDRS letters, during anti-VEGF treatment for nAMD. A total of 1,019 eyes received treatment during the study period, with severe vision loss occurring in 15.1 percent of patients after a median of six injections. Ranibizumab

(Continued from p. 52)

Refractive Pipeline

rolled in this multicenter, prospective, single arm, open-label, non-randomized clinical study. It'll include up to 334 operative eyes undergoing LASIK surgery for correction of hyperopia and hyperopic astigmatism.

"The demand for LASIK vision correction has risen significantly among our patients over the past few years, and refractive surgeons want options that meet the needs of their patients," said Y. Ralph Chu, MD, study investigator, and founder and medical director of Chu Vision Institute and Chu Surgery Center, Bloomington, Minnesota, in a prepared company statement discussing the trial. "This study represents an exciting opportunity to evaluate new technology that has the potential to help more hyperopic patients."

Refractive surgery continues to evolve with the addition of new and refined technologies, concludes Dr. Manche. "All of the current keratorefractive surgical procedures including LASIK, SMILE and PRK offer outstanding outcomes with excellent safety. We anticipate that new surgical procedures will continue to advance the field and improve outcomes and safety." ◀

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was injected in 52.8 percent of cases and aflibercept in 31.9 percent. The researchers reported that functional recovery after three months was significant and showed no further improvement at six months.

The researchers also reported better visual outcomes in eyes with no substantial central macular thickness changes compared with eyes that had an increase of >20 percent or a decrease of >5 percent in thickness.

The researchers say that, to their knowledge, this is the first real-life study exploring the incidence, OCT correlation and intermediate prognosis of severe visual acuity loss during anti-VEGF treatment in patients with nAMD. They found that a ≥15 ETDRS letter loss between two consecutive intravitreal injections wasn't unusual in patients receiving intravitreal injection treatment. Since the loss frequently occurred within nine months of diagnosis and two months after the last intravitreal injection, the physicians recommend close follow-up and a proactive regimen, at least in the first year.

Retina 2023; Mar 9. [Epub ahead of print].
Grassi MO, Monteleone G, Pozharitskiy N, et al.

Central Field Damage in Glaucomatous Eyes

Researchers characterized the relationship between deep-layer microvasculature dropout (MvD) and central visual field damage in primary open-angle glaucoma patients with and without high axial myopia, as part of a cross-sectional study.

Seventy-one eyes (49 patients) with high axial myopia and POAG and 125 non-highly myopic POAG eyes (97 patients) were enrolled. Presence, area and angular circumference of juxtapapillary MvD were evaluated on optical coherence tomography angiography B-scans and en face choroidal images.

Here are some of the findings:

- Juxtapapillary MvD was detected more often in the highly myopic POAG eyes (43 eyes, 86 percent) than in the non-highly myopic eyes (73 eyes, 61.9 percent; p=0.002).
- In eyes with MvD, the following were significantly larger in highly myopic eyes vs. non-highly myopic eyes:
  — MvD area (area [0.69; CI, 0.40, 0.98]) mm^2 vs. 0.31 (CI, 0.19, 0.42) mm^2; p=0.011) and
  — angular circumference (84.3 [CI, 62.9 to 105.8] vs. 74.5 [CI, 58.3 to 90.9]); p<0.001.
- 24-2 VF mean deviation was significantly worse in eyes with MvD compared with eyes without MvD in both groups (p<0.001).
- After adjusting for 24-2 MD VF, central visual field defects were more frequently found in eyes with MvD compared with eyes without MvD (82.7 vs. 60.9 percent; p<0.001).
- In multivariable analysis, higher intraocular pressure, worse 24-2 VF MD, longer axial length and greater MvD area and angular circumference were associated with worse 10-2 VF MD.

> **Researchers found microvascular dropout was more prevalent and larger in primary open-angle glaucoma eyes with high myopia than in non-highly myopic POAG eyes.**

Researchers found microvasculature dropout was more prevalent and larger in primary open-angle glaucoma eyes with high myopia than in non-highly myopic primary open-angle glaucoma eyes. In both groups, eyes with microvasculature dropout showed worse glaucoma severity and more central VF defects.

Br J Ophthalmol 2023; Feb 20. [Epub ahead of print].
Micheletti E, El-Nimri N, Nishida T, et al.

Retinal Effects of Combined Cornea/Cataract Procedures

Scientists evaluated alterations in central retinal thickness (CRT) and their implications for visual acuity after ultrathin Descemet's stripping automated endothelial keratoplasty (UT-DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK) combined with cataract surgery.

A total of 72 eyes of 72 patients with Fuchs' endothelial dystrophy and cataract were included and equally randomized to UT-DSAEK or DMEK. A control group of 40 eyes of 40 patients with cataract were included for cataract surgery. All participants were examined preoperatively, as well as three and six months postoperatively.

Here are some of the findings:

- No significant differences were reported in central retinal thickness between the study groups after surgery (p=0.896).
- A significant difference in best-corrected visual acuity progression over time was found between the study groups (p<0.0001).
- Average improvements of 8.03 EDTRS after UT-DSAEK (p<0.001) and 16.77 EDTRS after DMEK (p<0.001) were found six months postoperatively.
- No significant correlation was found between the change in best-corrected visual acuity and central retinal thickness from baseline to three months postoperatively (r^2<0.0001; p=0.96) and from baseline to six months postoperatively (r^2=0.0053; p=0.46).

Scientists wrote that central retinal thickness wasn't altered by ultrathin-Descemet's stripping automated endothelial keratoplasty, Descemet's membrane endothelial keratoplasty or cataract surgery three and six months postoperatively.

They added that the patients' best-corrected visual acuity significantly improved three months after UT-DSAEK and six months after DMEK. The investigators didn't find any significant correlations between the change in the subjects' best-corrected visual acuity and their central retinal thickness postoperatively. As such, the scientists concluded that CRT alterations were comparable after UT-DSAEK, DMEK and cataract surgery. ◀

Cornea 2023; Feb. 27. [Epub ahead of print].
Madsen M, Brok M, Anders I, et al.

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EDITED BY BONNIE SKLAR, MD

WILLS EYE RESIDENT CASE REPORT

A woman presents to the Wills Eye Emergency Room with suspected neuroretinitis.

ERIK MASSENZIO, MD, AND J.P. DUNN, MD
PHILADELPHIA

Presentation

A 69-year-old Caucasian female was referred to the Wills Eye Emergency Room for suspected neuroretinitis in her right eye. Three years prior, she had a "strange round rash" on her leg, which was associated with bilateral knee pain and swelling. Six months earlier, she noticed off-and-on joint pain in her left wrist. About one week prior to presentation, she noticed flashing lights and blurry vision in her right eye. She was diagnosed with neuroretinitis and treated with doxycycline. She then was referred to the Wills Eye Emergency room after her blurry vision worsened and her clinical picture remained uncertain.

Medical History

The patient had no significant past ocular history. Past medical history included hypothyroidism for 40 years. Family history included glaucoma in multiple family members, age-related macular degeneration in her mother, hypertension in her father, brother and sister; and rheumatoid arthritis in her mother.

Current medications included levothyroxine, vitamin D3, desloratadine, magnesium chloride and doxycycline.

Examination

Ocular examination demonstrated visual acuity of 20/400 in the right eye and 20/20 in the left eye. Pupils were pharmacologically dilated at the time of examination, but no APD was noted by the referring physician. Intraocular pressure was 12 and 15 mmHg in the right and left eyes, respectively. Confrontation visual fields were notable for inferotemporal and superonasal deficits in the right eye. Extraocular motility was full bilaterally. Color plates were 0/8 without recognition of the test plate in the right eye, and 8/8 in the left. Anterior segment examination was notable for decreased tear breakup time and 2+ nuclear sclerosis bilaterally.

Dilated fundus examination of the right eye demonstrated 360 degrees of disc margin blurring, peripapillary edema extending into the macula, and tortuous vessels in the right eye. A small flat nevus was noted near the inferior arcade in the right eye (*Figure 1*).

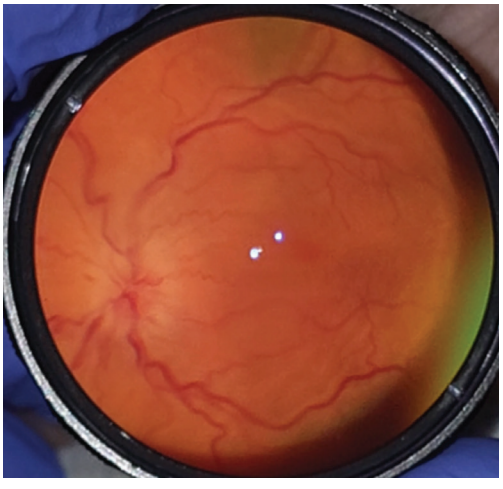

Figure 1. Clinical photo.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears on the next page.

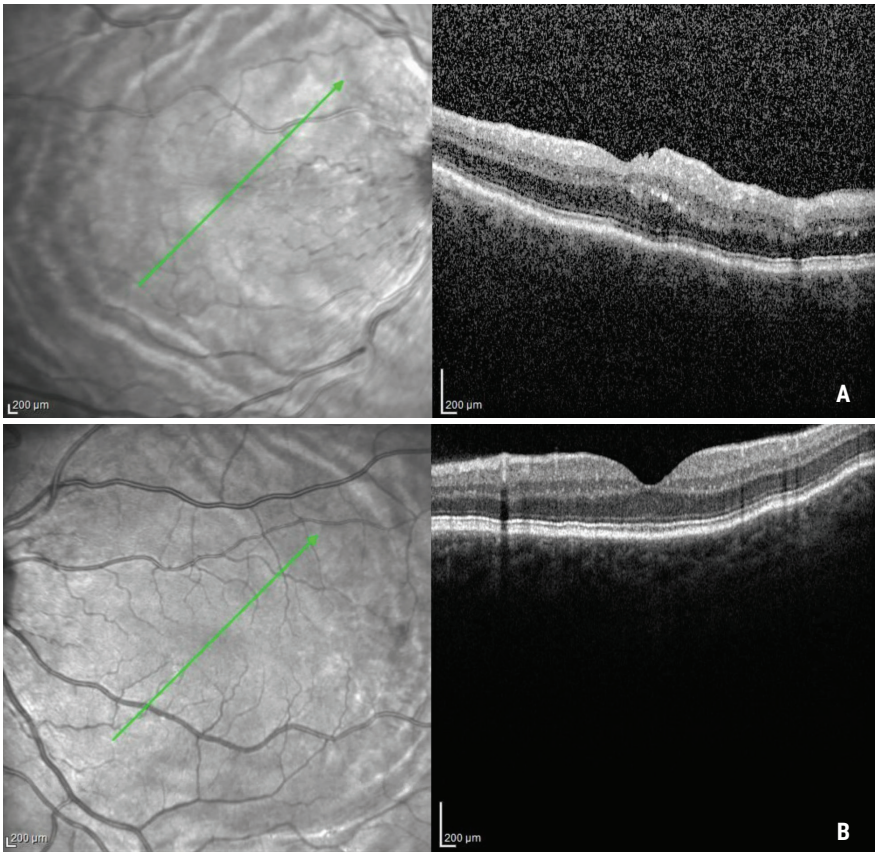

Figure 2. OCTs of the right (A) and left (B) eyes demonstrating choroidal folds.

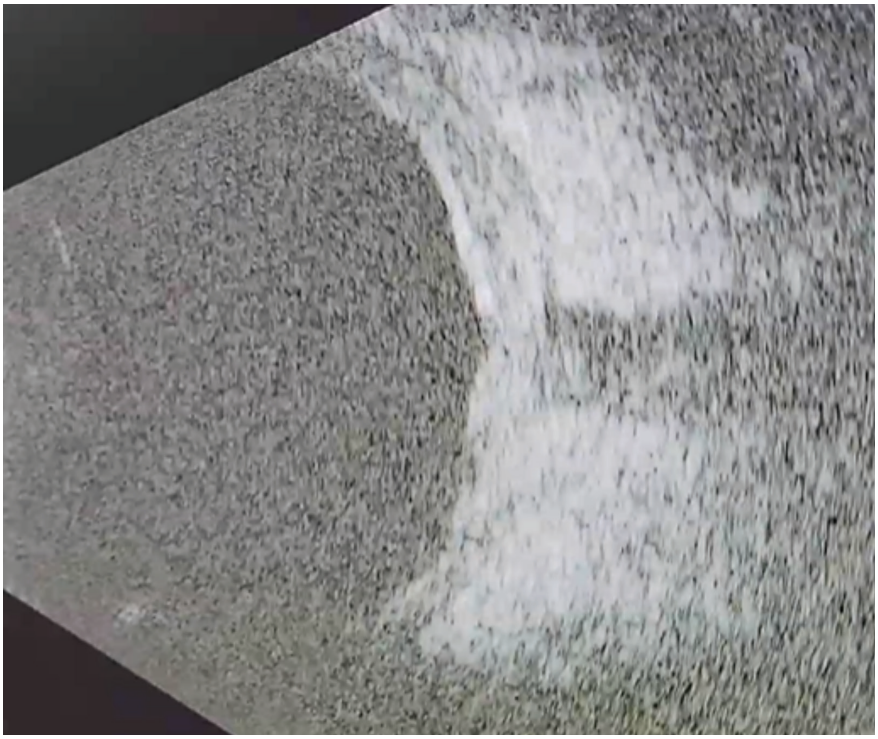

Figure 3. B-scan ultrasonography of a representative patient with sclero-choroidal thickening and a "T" sign representing sub-Tenon's edema.

Work-up, Diagnosis and Treatment

Brain and orbital MRI with and without contrast revealed mild bilateral perioptic enhancement. The updated differential diagnosis included vascular, inflammatory, infectious and neoplastic etiologies.

The laboratory work-up included ACE, ANCA, Quantiferon Gold, syphilis, Lyme, toxoplasma, and *Bartonella* serologies, all of which were negative. A lumbar puncture was negative for infectious etiologies, as well as NMO and MOG. A chest X-ray was unremarkable.

> **Optical coherence tomography demonstrated optic disc edema with significant thickening of the peripapillary retina in the right eye, and choroidal folds in both eyes.**

She was admitted to Wills Eye Hospital for intravenous methylprednisolone 250 mg every six hours. During admission, the patient's visual acuity improved from 20/400 to 20/200. Optical coherence tomography and B-scan ultrasound images were obtained. Optical coherence tomography demonstrated optic disc edema with significant thickening of the peripapillary retina in the right eye, and choroidal folds in both eyes *(Figure 2)*. B-scan revealed a "T" sign in the right eye, and sclero-choroidal thickening in the left eye *(Figure 3)*.

A diagnosis of posterior scleritis in the right eye was made and she was started on an oral prednisone 60 mg taper. The patient was

referred to a rheumatologist who ordered an extensive laboratory workup which was unrevealing. CT scan was performed without evidence of lung parenchymal abnormalities.

Based on the patient's family history of rheumatoid arthritis and personal history of arthralgias and joint swelling, suspicion for an undifferentiated autoimmune disease remained high despite a negative work-up.

Discussion

As William Benson, MD, recalled in his review of posterior scleritis,[1] Peter Watson once remarked "posterior scleritis must be one of the most underdiagnosed treatable conditions in ophthalmology, partly because its manifestations are so protean and partly because the diagnosis is rarely considered."[1] Dr. Benson notes some of the varied presentations of posterior scleritis, including a circumscribed fundus mass, choroidal folds, retinal striae, disc edema, annular choroidal detachment, exudative macular detachment, cystoid macular edema and peripheral retinal detachment. In many cases of posterior scleritis, pain may be minimal or absent.[1-4] Diagnosis is usually made with B-scan ultrasonography when a "T" sign is noted, which is caused by edema in the sub-Tenon's space near the optic nerve head; however, it must be noted that other causes of posterior inflammation such as inflammatory orbital pseudotumor can cause a "T" sign.[5-7]

> **Diagnosis is usually made with B-scan ultrasonography when a "T" sign is noted, which is caused by edema in the sub-Tenon's space near the optic nerve head.**

Our patient had bilateral choroidal folds. While the right eye was symptomatic, the left eye didn't have any decreased vision or pain. The differential diagnosis of choroidal folds includes posterior scleritis, neoplasms, papilledema, hypotony, Graves' disease, macular degeneration and hyperopia.[1,8-10]

In a case comparison of unilateral to bilateral cases of choroidal folds by Alan Leahey, MD, and colleagues, the most common causes of bilateral choroidal folds included macular degeneration, hyperopia and "idiopathic."[11] It's been hypothesized that "idiopathic" or "undifferentiated" choroidal folds actually may represent previous posterior scleritis or "silent" scleritis. Another study found that 83 percent of patients with "idiopathic" choroidal folds also had an underlying autoimmune condition such as rheumatoid arthritis, lupus or Crohn's disease.[12] Our patient's asymptomatic choroidal folds may have been caused by a previous bout of silent posterior scleritis, especially since no hyperopia or macular degeneration were present.

In conclusion, posterior scleritis should be considered even in patients without the classic symptoms and signs on clinical examination. In addition, bilateral choroidal folds can be found in patients with macular degeneration, hyperopia and hypotony; however, it's possible that some idiopathic causes of bilateral choroidal folds may represent silent or previous scleritis from an underlying autoimmune disease. When encountering a patient with undifferentiated posterior pathology, a B-scan can help rule in or rule out this under-considered and underdiagnosed condition. ◀

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SYFOVRE ™ (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye

Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization

Punctate keratitis included: punctate keratitis, keratitis

Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

The safety and effectiveness of SYFOVRE in pediatric patients have not been established.

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing neovascular AMD, endophthalmitis, and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-17Feb2023-1.0

2/23 US-PEGGA-2200163 v2.0

NOW APPROVED: the first and only FDA-approved treatment for GA secondary to AMD[1]

GA unravels so much

Save retinal tissue by slowing progression[1–3]

INDICATION

SYFOVRE™ (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

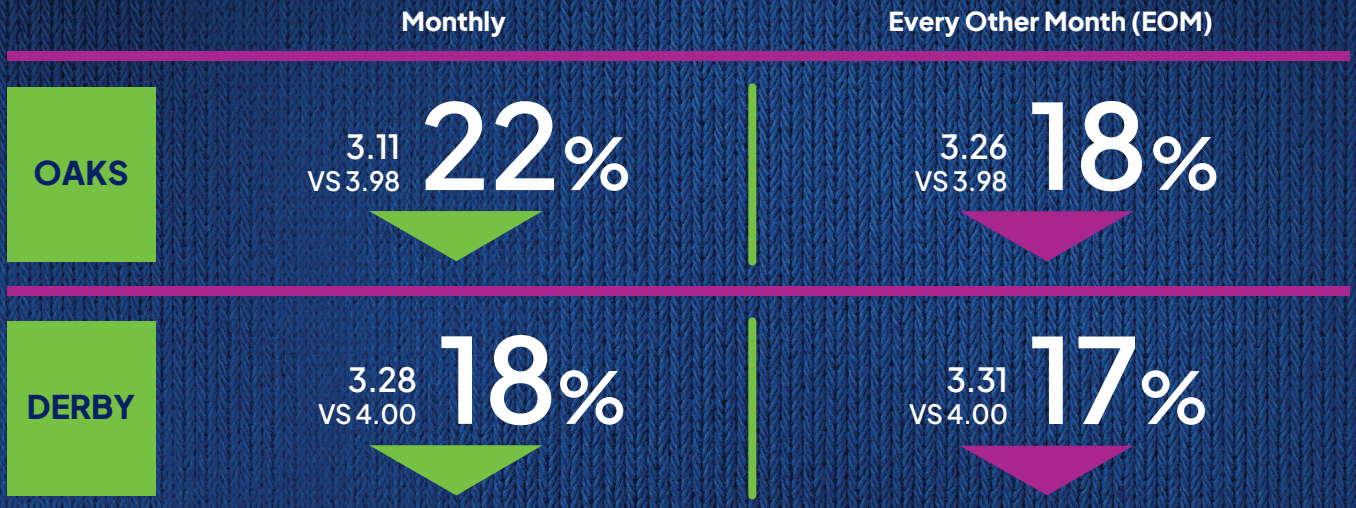
CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1] Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]
AMD=age-related macular degeneration; GA=geographic atrophy; SE=standard error.

Explore more at SyfovreECP.com

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24–month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

Apellis

2/23 US-PEGGA-2200051 v1.0

SYFOVRE™
(pegcetacoplan injection)
15 mg / 0.1 mL

FOR REFRACTORY GLAUCOMA

XEN® helps put the power to control her IOP in your hands

Not actual patients.

The XEN® Gel Stent is minimally invasive filtering surgery that achieves powerful reduction of intraocular pressure (IOP).[1,2]

- From a wide range of baseline pressures,* XEN® achieved a mean IOP of 15.9 (± 5.2) mm Hg through 12 months (n = 52)[1,2]
- 76% of XEN® patients achieved a ≥ 20% IOP reduction in the ITT group (N = 65)[1]
- 81% of XEN® patients achieved a ≥ 25% IOP reduction among those completing the 12-month visit (n = 52)[2]
- Pivotal safety data included 0% intraoperative complications (0/65) and 0% persistent hypotony (0/65); transient hypotony† occurred in 24.6% of patients (16/65)[1]

ITT = intent to treat.

*In the XEN® clinical study, baseline medicated IOP ranged from 20.0 to 33.7 mm Hg.[2]

†No clinically significant consequences were associated with hypotony, such as choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy. IOP < 6 mm Hg was defined as an adverse event, regardless of whether there were any associated complications or sequelae related to the low pressure. Thirteen cases occurred at the 1-day visit; there were no cases of persistent hypotony, and no surgical intervention was required for any case of hypotony.[1]

THINK XEN® AT THE POINT OF YOUR SURGICAL DECISION.

INDICATIONS

The XEN® Glaucoma Treatment System (XEN® 45 Gel Stent preloaded into a XEN® Injector) is indicated for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open-angle glaucoma, and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XEN® Gel Stent is contraindicated in angle-closure glaucoma where angle has not been surgically opened, previous glaucoma shunt/valve or conjunctival scarring/pathologies in the target quadrant, active inflammation, active iris neovascularization, anterior chamber intraocular lens, intraocular silicone oil, and vitreous in the anterior chamber.

WARNINGS

XEN® Gel Stent complications may include choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention, and intraocular surgery complications. Safety and effectiveness in neovascular, congenital, and infantile glaucoma has not been established. Avoid digital pressure following implantation of the XEN® Gel Stent to avoid the potential for implant damage.

PRECAUTIONS

Examine the XEN® Gel Stent and XEN® Injector in the operating room prior to use. Monitor intraocular pressure (IOP) postoperatively and if not adequately maintained, manage appropriately. Stop the procedure immediately if increased resistance is observed during implantation and use a new XEN® system. Safety and effectiveness of more than a single implanted XEN® Gel Stent has not been studied.

ADVERSE EVENTS

The most common postoperative adverse events included best-corrected visual acuity loss of ≥ 2 lines (≤ 30 days 15.4%; > 30 days 10.8%; 12 months 6.2%), hypotony IOP < 6 mm Hg at any time (24.6%; no clinically significant consequences were associated, no cases of persistent hypotony, and no surgical intervention was required), IOP increase ≥ 10 mm Hg from baseline (21.5%), and needling procedure (32.3%).

Caution: Federal law restricts this device to sale by or on the order of a licensed physician. For the full Directions for Use, please visit www.allergan.com/xen/usa.htm or call 1-800-678-1605. Please call 1-800-433-8871 to report an adverse event.

Please see accompanying full Directions for Use or visit https://www.rxabbvie.com/pdf/xen_dfu.pdf

Allergan an AbbVie company

US-XEN-230003 01/2023 020627

References: 1. XEN® Directions for Use.
2. Data on file, Allergan, 2016; Clinical Study Report R-020.

XEN® GEL STENT

A Powerful, Proven Procedure